Supreme Court, U.S.
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IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON PETITION FOR A WRIT OF CERTIORARI
TO THE SUPREME COURT OF THE STATE OF VERMONT

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

Whether the prescription drug labeling judgments imposed on manufacturers by the Food and Drug Administration ("FDA") pursuant to FDA's comprehensive safety and efficacy authority under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, preempt state law product liability claims premised on the theory that different labeling judgments were necessary to make drugs reasonably safe for use.

LIST OF PARTIES

Pursuant to Rule 14.1(b), the following list identifies all of the parties to the appellate proceeding in the Supreme Court of Vermont, whose judgment is sought to be reviewed:

A. Petitioner

Wyeth

B. Respondent

Diana Levine

CORPORATE DISCLOSURE STATEMENT

Petitioner Wyeth has no parent corporation, and no publicly held company owns 10% or more of its stock.

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The decision of the Supreme Court of Vermont is reported at -- A.2d -- (Vt. 2006) and reprinted in the Appendix ("App.") at 1a-48a. The trial court's decision denying Petitioner's Motion for Judgment as a Matter of Law is reprinted at App. 49a-74a.

JURISDICTION

The Supreme Court of Vermont rendered its decision on October 27, 2006, App. 1a, and denied a timely motion for reargument on December 11, 2006, App. 75a. This Court has jurisdiction under 28 U.S.C. § 1257(a).

PERTINENT CONSTITUTIONAL, STATUTORY, AND REGULATORY PROVISIONS

The pertinent constitutional, statutory, and regulatory provisions are set forth in the Appendix, App. 77a-138a.

INTRODUCTION

Granting this petition would enable the Court to resolve the pervasive and recurring conflict between state claims of power to regulate prescription drug labeling and the integrity of the congressionally mandated federal prescription drug labeling regime that lies at the heart of the Food and Drug Administration's ("FDA's") regulatory authority. This conflict is currently at issue in tens of thousands of cases in our nation's courts, in which plaintiffs claim that manufacturers should have modified FDA-approved prescription drug labeling. The lower courts have resolved this conflict inconsistently and have given varying weight to FDA's formal statements on the extent to which such claims obstruct its regulatory objectives. A ruling by this Court on the preemption issues presented would provide invaluable guidance to the hundreds of federal and state judges now grappling with these claims.

In this case, Wyeth's federally approved labeling of its anti-nausea drug Phenergan reflected FDA's expert judgment that the option to administer the drug intravenously by direct, or

"push," ("IV push") injection[1] – which provides faster and more potent relief than other methods of administration – should be preserved. Respondent was injured when Phenergan was administered to her by IV push injection and somehow came in contact with arterial blood, causing gangrene and the loss of her forearm. App. 2a. The approved labeling repeatedly and prominently warned of the hazard of arterial exposure, expressly stating that, should a health care provider determine that IV push injection was warranted, he or she must use "extreme care" not to introduce the medicine into the patient's arteries to avoid serious injuries, including "gangrene requiring amputation," which was "likely under such circumstances." App. 167a. Respondent claimed that Phenergan's labeling should have gone further and foreclosed IV push injection altogether in light of the risk of injury. Wyeth countered that Respondent's claim was preempted under federal law.

Over the strong dissent of Chief Justice Reiber, a Vermont Supreme Court majority held that Respondent's claim was not preempted by FDA's decisions to preserve the IV push injection option because Wyeth was not absolutely barred from implementing labeling changes without FDA's prior approval. The majority reasoned that Wyeth could have – and, as the jury found, should have – foreclosed IV push injection. It also declined to consider Wyeth's contention that the duty to bar IV push injection imposed by Vermont law would obstruct the purposes and objectives of FDA's supervision of Phenergan's labeling, concluding that this line of traditional preemption analysis was precluded by a savings clause in the Federal Food, Drug and Cosmetic Act ("FDCA"). App. 21a-24a. In reaching its decision, the majority rejected FDA's unequivocal position that claims precisely like Respondent's disrupted the agency's ability to ensure that prescribers receive the best information on how to balance the risks and benefits of methods of drug administration. App. 24a-28a.

[1] IV push injections are administered by applying pressure to inject a drug into a patient's veins and differ from "IV drip" administration, where a drug is slowly "dripped" into a patient's veins from a hanging IV bag.

The Vermont Supreme Court's decision is in error. If allowed to stand, it would empower courts to review and override FDA's careful and comprehensive balancing of safety and effectiveness concerns in prescription drug labeling and to undermine the integrity of FDA's statutorily mandated labeling regime – as the expert agency has recognized. This Court should grant review to restore the proper balance between federal and state authority in this critical area affecting the nation's public health.

STATEMENT OF THE CASE

A. Factual Background

1. FDA Regulatory Regime

Congress has established FDA as the sole federal agency commissioned both to "protect the public health" by ensuring that drugs are safe and effective and to "promote the public health" by ensuring prompt public access to drugs it has found to be safe and effective. 21 U.S.C. § 393(b). FDA's power to ensure the safety of drugs and their labeling dates back to the 1938 Federal Food, Drug and Cosmetic Act ("FDCA"), in which Congress first charged FDA to: (a) serve as the sole gatekeeper for deciding whether a drug is safe for its labeled uses and includes "adequate directions for [such] use"; and (b) seize drugs it finds are inadequately labeled or dangerous when used as intended. *See* Pub. L. No. 75-717, §§ 201(p), 301(a), 502(f), 505(d)(1), 52 Stat. 1040, 1041-42, 1051-52 (1938) (codified as amended at 21 U.S.C. §§ 321(p), 331(a), 352(f), 355(d)). Marketing a prescription drug with a label that is not FDA-approved is a federal crime. *See* 21 U.S.C. §§ 332(a), 333(a), 334.

Since 1962, Congress also has entrusted FDA with ensuring that safe drugs are effective for their labeled uses. *See* Drug Amendments of 1962, Pub. L. No. 87-781, § 102(b), 76 Stat. 780, 781 (1962) (codified as amended at 21 U.S.C. § 355(b)). This significant expansion of FDA's regulatory oversight authority recognized that the use of any drug entails some risk and that marketing approval should rest on FDA's scientific determination that a drug's overall health care benefit outweighs its risks. *See* S. Rep. No. 87-1744, at 15 (1962), *as reprinted in*

1962 U.S.C.C.A.N. 2884, 2891-92 (observing that, for very risky drugs, "the determination of safety is, in the light of the purposes of the new drug provisions, considered by [FDA] to be inseparable from consideration of the drug's effectiveness"); Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006), App. 128a ("Under the Act and FDA regulations, the agency makes approval decisions based . . . on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling." (citation omitted)). Balancing risks against benefits for particular prescription drugs, dosages, and methods of administration thus has been the central task of FDA for nearly a half-century.

As FDA has repeatedly made clear, the agency conducts this risk-benefit assessment from a forward-looking perspective, with the overall public health in mind, rather than through the prism of individual cases. As a former Commissioner has testified:

> Every time the scientists on our staff allow a new drug to come to market, they have to take the sum total of scientific knowledge that they can muster about the drug, and reach a conclusion as to whether or not the good that the drug will do, the lives it will save or the suffering that it will prevent, outweighs the known side-effects.

See Hearing on H.R. 6245 Before the Subcomm. On Antitrust of the H. Comm. On the Judiciary, 87th Cong. 135 (1962) (statement of George P. Larrick, Commissioner, FDA); *see also* FDA, *Draft Guidance for Industry: Development and Use of Risk Management Action Plans* 4 (Mar. 2005), *available at http://www.fda.gov/cder /guidance/6358fnl.pdf* (describing FDA's risk-benefit assessment as measuring whether, under labeled conditions of use, "the clinical significance and probability of [a drug's] beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects").

To obtain FDA approval of a new prescription drug, the manufacturer must submit a New Drug Application ("NDA"). *See* 21 U.S.C. § 355(b). As part of the NDA, the manufacturer

must submit comprehensive information concerning the new drug, "full reports of investigations" concerning safety and effectiveness, and "specimens of the labeling proposed to be used for such drug." *Id.* § 355(b)(1); 21 C.F.R. § 314.50. The information submitted must establish that the new drug is safe and effective "for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof" before FDA will approve it for distribution and marketing. 21 U.S.C. § 355(d)(1).

The review and approval of a drug's labeling therefore is a critical means through which FDA carries out its risk-benefit assessment. *See* New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985) ("Drug labeling serves as the standard under which FDA determines whether a product is safe and effective."); *see also* FDA, *Guidance: Drug Safety Information – FDA's Communication to the Public* 7 (Mar. 2007), *available at* http://www.fda.gov/cder/guidance/7477fnl.pdf ("FDA-approved drug product labeling is the primary source of information about a drug's safety and effectiveness . . . ."). For this reason, FDA has issued a series of regulations that comprehensively dictate the form and substance of all prescription drug labels. Those drug labels must include, among a host of other requirements, "a summary of the essential scientific information needed for safe and effective use of the drug," 21 C.F.R. § 201.56(1), including a description of "clinically significant adverse reactions," "other potential safety hazards," "limitations in use imposed by them, . . . and steps that should be taken if they occur," *id.* § 201.57(c)(6)(i). Accordingly, FDA's approval of an NDA is inseparable from the agency's approval of the precise language contained on the new drug's label. *See id.* § 314.50(e)(2)(ii), (*l*)(1)(i).

FDA's regulatory authority over prescription drug labeling continues after a drug is initially approved for marketing and distribution. Manufacturers have an ongoing obligation to submit reports "of data relating to clinical experience" –

including adverse drug events. 21 U.S.C. § 355(k)(1); *see also* 21 C.F.R. § 314.80. FDA has the authority to withdraw a drug from the market if it concludes the drug is unsafe or ineffective for its labeled uses. *See* 21 U.S.C. § 355(e). Although manufacturers may initiate labeling changes, they must submit to FDA full descriptions of all proposed changes and ordinarily await FDA approval before implementing a proposed change. *See id.* § 355(b)(1)(F); 21 C.F.R. § 314.70. FDA has, however, adopted a regulation – known as the "change being effected," or "CBE," provision – that extraordinarily allows manufacturers to initiate interim post-approval labeling changes pending FDA approval. The CBE provision is designed to operate only when scientifically significant, newly discovered information demands changes to: (a) add or strengthen a contraindication, warning, precaution, or adverse reaction; or (b) add or strengthen an instruction about dosage and administration intended to increase safe use of a drug. *Id.* § 314.70(c)(6)(iii)(A), (C). CBE changes are interim; "the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act." 71 Fed. Reg. at 3934, App. 132a.

2. FDA's Regulation of Phenergan

Wyeth sold injectable Phenergan for treatment of nausea. FDA found injectable Phenergan safe for labeled conditions of use and approved it for sale with no limitation on any method of IV injection in 1955. In 1967, Wyeth first received a report of gangrene and subsequent amputation resulting from arterial blood exposure to Phenergan, which it reported to FDA. App. 139a. At that time, Phenergan's labeling already warned against such arterial blood exposure through perivascular extravasation or intra-arterial injection.[2] App. 139a-140a.

Between 1967 and 1981, FDA worked closely with Wyeth

[2] Perivascular extravasation occurs when a drug administered intravenously leaks out of the vein into the surrounding tissue, where it may come into contact with arterial blood. App. 4a, 42a. Perivascular extravasation occurs through no fault of the physician or the drug manufacturer. App. 42a.

through a series of communications and at least one in-person meeting to refine Phenergan's warnings with respect to IV push administration. As of at least 1974, Phenergan's label made clear that intramuscular ("IM") injection was the "preferred parenteral route of administration" and advised that IV administration was "well-tolerated" but "not without some hazard" because gangrene could result from exposure of Phenergan to arterial blood. App. 53a.

As of 1981, the Phenergan label included the following language: "When administering any irritant drug intravenously, it is usually *preferable* to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily" — *i.e.*, through IV drip administration. App. 54a (emphasis added). While FDA noted its preference for the IV drip method, it never suggested that the IV push method of injection should be contraindicated or foreclosed.

In 1987, after Wyeth complied with a general FDA mandate to reformat Phenergan's labeling and submit it by a supplemental New Drug Application ("sNDA") for approval, FDA recommended revisions concerning the "recognition and management of unintended intra-arterial injection." App. 150a-157a. These changes included an enhanced instruction concerning IV drip administration: "Injection through a properly running intravenous infusion [set] may enhance the possibility of detecting arterial placement. In addition, this results in delivery of a lower concentration of any arteriolar irritant." App. 152a. Again, however, FDA never suggested that the IV push method should be contraindicated or foreclosed.

On May 3, 1988, Wyeth submitted new draft labeling for FDA approval that essentially incorporated FDA's recommended changes relating to IV drip administration: "Injection into an intravenous infusion set that is known to be running properly should decrease the possibility of inadvertently injecting

promethazine intra-arterially. In addition, this results in delivery of a lower concentration of any arteriolar irritant." App. 54a.

In 1997 – explaining that it had taken extra time to review Phenergan's proposed labeling changes to ensure that it had "dotted every 'i' and crossed every 't'" – FDA specifically ordered Wyeth to "[r]etain [the] verbiage in [the] current label" concerning inadvertent intra-arterial injection and to make other labeling changes. App. 158a-159a, 162a. Wyeth submitted a revised draft package insert on May 8, 1998 in compliance with FDA's orders. FDA then approved that labeling and expressly commanded Wyeth that "[t]he final printed labeling (FPL) for the package insert *must be identical to the draft package insert submitted May 8, 1998*." App. 165a (emphasis added).

FDA's consistent decision not to foreclose IV push administration of Phenergan reflected a classic balancing of risks and benefits. The beneficial effects of IV injection generally begin within five minutes; IV drips (when equipment is available) are slower to administer, and IM injection can require twenty minutes or more to take effect. App. 165a. This is no small difference: extreme nausea can cause a patient to lose fluids quickly, which leads to dehydration, a serious medical condition. A doctor, confronted with a patient in dire need of relief from nausea, could reasonably decide that the benefits of IV push administration would warrant taking its increased risk.[3]

3. The Operative Phenergan Label when Respondent Was Treated

In 2000, as a result of the foregoing FDA oversight over a 45-year period and a series of revisions, Phenergan's two-page label included repeated, prominent notice of the risk of gangrene arising from inadvertent arterial exposure in no fewer than four

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[3] Moreover, under certain circumstances, IM injection is unreliable or ineffective, such as in the treatment of overweight patients and patients with poor blood flow to the various muscle groups due to dehydration or cardiac disease. In such a situation, a doctor could determine that IV push injection is the only way to provide the patient with the needed relief.

separate sections – *i.e.*, "Contraindications," "Warnings," "Adverse Reactions," and "Dosage and Administration." Two such sections provided the following notice in upper-case type:

> **INADVERTENT INTRA-ARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY.**

App. 4a, 167a. The label further warned that:

> Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injection of Phenergan Injection, usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances.

App. 4a, 167a. The label also included lengthy instructions concerning the means of minimizing this risk in both the "Dosage and Administration" and "Warnings" sections. App. 167a.

4. The Administration of Phenergan to Respondent

On April 7, 2000, Respondent sought treatment from Northeast Washington County Community Health, Inc. (the "Health Center") for a severe migraine headache and associated nausea and dehydration. App. 2a. Respondent was initially treated with Phenergan via IM injection, the preferred method of administration. App. 2a.

Respondent returned to the Health Center later that day because she had not obtained effective relief. App. 2a. A second dose of Phenergan was then administered directly into Respondent's vein via IV push injection. App. 2a. Phenergan's FDA-approved label specifically instructed practitioners to proceed with extreme caution in any administration; the administering physician assistant was aware of these instructions and of the risk of arterial exposure through misinjection.

Respondent thereafter developed the symptoms of arterial exposure and had to have her forearm amputated. App. 2a. Before the commencement of this case, Respondent sued the health care providers for malpractice and settled for $700,000.

B. Proceedings Below

1. The Trial Court Proceedings

Respondent brought state-law-based liability claims against Wyeth on the theory that Wyeth should have revised Phenergan's FDA-approved label to bar IV push administration. App. 38a, 41a. The jury returned a verdict in favor of Respondent, who was ultimately awarded $ 6,774,000. App. 3a.

Wyeth sought judgment as a matter of law on the ground that federal law preempted Respondent's claims. The trial court denied Wyeth's motion, issuing an opinion independently addressing preemption as a matter of law. App. 4a, 74a. In its view, FDA's CBE regulation, 21 C.F.R. § 314.70, "permit[s] strengthened warnings without approval on an interim basis," App. 64a, such that Wyeth could be required to conform its labeling to common law tort duties. The court acknowledged the inevitable differences between FDA's comprehensive balancing of public safety and efficacy interests and the tort process, which views "the matter in hindsight through the lens of a single catastrophic case," App. 62a, but still found that the jury's state-law-based judgment presented no obstacle to FDA's regulatory objectives, App. 63a.

2. The Appeal to the Vermont Supreme Court

Wyeth timely appealed to the Vermont Supreme Court. Wyeth contended that the trial court erred, *inter alia*, by failing to hold that Respondent's common law claims were preempted because: (1) Wyeth would have been unable to comply with both Vermont's common law duty to foreclose IV push injection and FDA's directive, as evidenced by the drug's approved label, to retain it; and (2) the claims would obstruct the full accomplishment of FDA's risk-benefit objective to optimize use of Phenergan by imposition of a duty to foreclose IV push injection. App. 5a-6a. The Vermont Supreme Court rejected both

arguments and affirmed the trial court's decision. App. 19a, 28a.

The court first rejected Wyeth's claim that it would be impossible for Wyeth to comply with both a Vermont common law duty to foreclose IV push injection and a federal duty to use an FDA-approved label that allowed the drug to be administered in this fashion. Like the trial court, the Supreme Court relied on the CBE regulation, 21 C.F.R. § 314.70(c). In the court's view, "FDA approval of a particular label does not preempt a jury finding that the label provided insufficient warning, as defendant was free under § 314.70(c) to strengthen the warning without prior FDA approval." App. 17a. The court also declined to accord any significance to FDA's directive to Wyeth to "[r]etain verbiage in current label." App. 17a.

The court next refused to consider Wyeth's claim that Vermont's decision to impose a state tort law duty on Wyeth created an obstacle to the objectives of the FDA regulatory regime. The court held that all such "obstacle" preemption claims were foreclosed by language in the 1962 amendments to the FDCA that premised preemption on a "direct and positive conflict between such amendments and [a] provision of State law." App. 21a (quoting Drug Amendments of 1962, § 202, 76 Stat. at 793, App. 112a). The court reasoned that section 202 restated the standard for "impossibility" preemption and thus "remove[d] from . . . consideration the question of whether common-law tort claims present an obstacle to the purposes and objectives of Congress." App. 21a.

Last, the court refused to give any weight to FDA's formal preemption analysis. Specifically, in a regulatory preamble to recent amendments to its labeling rule, FDA rejected the positions adopted by many federal courts and the Vermont Supreme Court that (1) section 314.70 broadly permits manufacturers to make unilateral labeling changes and (2) "[s]tate law serves as an appropriate source of supplementary safety regulation for drugs by encouraging or requiring manufacturers to disseminate risk information beyond that required by FDA under the act." App. 24a (quoting 71 Fed.

Reg. at 3934, App. 126a). To the court, FDA's analysis was "neither an authoritative interpretation of an ambiguous statutory provision entitled to deference, nor a persuasive policy statement entitled to respect." App. 28a (internal citation omitted).

Chief Justice Reiber dissented. The Chief Justice first concluded that an "actual conflict" existed between the jury verdict and federal law because "the FDA clearly addressed the risks attending IV administration of the drug[,] . . . approved IV administration generally, and specifically warned of the dangers of direct IV administration, including inadvertent arterial injection possibly resulting in amputation." App. 38a. "These assessments are, in fact, the very essence of the FDA's approval and are in furtherance of the federal objective of advancing public health by balancing the risks and benefits of new drugs and facilitating their optimal use." App. 38a.

The Chief Justice also found that Wyeth was not "'free' to change drug labels under [section] 314.70" because the purpose of this regulatory provision "is to allow manufacturers to address newly discovered risks." App. 39a-40a. Here, not only was there a complete absence of new evidence concerning IV push administration of Phenergan, but "FDA had already evaluated the risk of inadvertent arterial injection . . . and had mandated warning language for the label to reflect that risk assessment" in its 1997 directive to Wyeth. App. 40a. Wyeth thus "could not both list all forms of IV administration as an approved use, as required by the FDA, and exclude all or some forms of IV administration as unsafe, as required by the jury's verdict in this case." App. 43a.

The Chief Justice next rejected the majority's view that the section 202 "direct and positive conflict" language forbade the court from assessing whether state tort law obstructed the federal purposes and objectives served by FDA's regulatory regime. App. 44a-45a. On the merits of Wyeth's argument, the Chief Justice concluded that "obstacle preemption" applied in this case under the reasoning of *Geier v. American Honda Motor Co.*, 529 U.S. 861 (2000). App. 45a. The Chief Justice

analogized the federal safety standard at issue in *Geier* – which "allow[ed] a choice of passive restraint systems while not mandating any particular system" and "was a deliberate decision that reflected a balance of diverse policy concerns" – with FDA's risk-benefit balancing judgment, which "considers various policy factors that are sometimes in tension with one another" to "maximize the availability of beneficial treatments." App. 48a. According to the Chief Justice, FDA's conclusion that "Phenergan is safe and effective when delivered through IV administration" preempts any tort duty that would require Wyeth to bar that particular use. App. 48a.

REASONS FOR GRANTING THE PETITION

The Vermont Supreme Court held that a manufacturer may be liable under state law for failing to bar a particular method of administration of a prescription drug. The federal agency expert in evaluating the safety and efficacy of drugs had concluded that this highly potent method of administration should remain available and directed the manufacturer to retain a label that, while urging prescribers to use extreme care in administering the drug, nonetheless retained it as a medical option. This case thus presents a direct conflict between the considered labeling decision of a federal agency exercising its *ex ante* responsibility to make comprehensive public health judgments and an *ex post* case-specific determination of one state jury that the federally approved labeling was inadequate.

Unfortunately, this conflict is far from uncommon. There are tens of thousands of individual claims, and potentially millions of class action claims, currently pending in the lower federal and state courts, in which plaintiffs contend that a manufacturer's use of FDA-approved labeling for its prescription drug is inadequate to satisfy state-law duties to warn.[4] Divided lines of authority already have emerged and are

[4] *See, e.g., In re Bextra & Celebrex Marketing, Sales Practices & Prods. Liab. Lit.*, No. 05-cv-01699-CRB (N.D. Cal.) (litigation consists of over 1,800 lawsuits); *In re Prempro Prods. Liab. Litig.*, No. 4:03CV01507 (E.D. Ark.); *In re Vioxx Marketing, Sales Practices &* (Cont'd)

highly unlikely to be reconciled by further lower court decisions. By deciding key preemption issues here on a record that squarely and cleanly presents them,[5] this Court can forestall erroneous decisions in numerous cases and the huge expenditure of resources required to correct those errors and reprocess the underlying cases.

The Vermont Supreme Court made basic and fundamental doctrinal errors in its preemption analysis. Wyeth has consistently argued that a jury verdict premised on the alleged inadequacy under state law of an FDA-approved prescription drug label is preempted when it "actually conflicts" with the federal drug labeling regime. State law "actually conflicts" with federal law when "compliance with both federal and state regulations is a physical impossibility," *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963), or when state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941). These bedrock principles apply with equal force to federal regulations, *see Fidelity Federal Savings & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153 (1982), and do not differentiate between common law rules arising from state jury verdicts and positive legislative enactments, *see Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 522 (1992). Prescription drug labeling cases implicate both species of conflict preemption.

Determining whether state tort claims "actually conflict"

(Cont'd)

Prods. Liab. Litig., No. 05-MDL-1657 (E.D. La.) (approximately 27,400 lawsuits, including over 46,100 plaintiff groups, and approximately 264 putative class actions as of December 2006). Individual suits like that presented here are almost too numerous to count.

[5] This case presents an ideal vehicle for resolving these legal issues because the facts underlying the preemption question are not in dispute. There is no allegation that Wyeth had failed to react to safety information not considered by FDA or that Wyeth breached any other state law duty that might make the Vermont Supreme Court's mistaken preemption analysis insufficient to reverse the judgment.

with FDA prescription drug labeling rules requires resolution of three key legal questions. *First*, does FDA's labeling regime developed under congressional mandate provide only a minimum safety standard open to unlimited state supplementation or a fully calibrated risk-benefit balance of national applicability that state law should not disrupt? *Second*, are principles of "obstacle" conflict preemption trumped in prescription drug cases either by a presumption against preemption or by a statutory requirement that preemption arise from a "direct and positive" conflict? *Third*, should weight be given in the preemption analysis to FDA's recent formal assessment of the adverse impact of tort actions on the integrity of its labeling regime?

The Vermont Supreme Court answered all of these questions incorrectly. *First*, it concluded – contrary to the agency's view of its own regulations – that FDA's labeling requirements merely provided a "floor" and that a manufacturer was free unilaterally to change its labeling without prior FDA approval. *Second*, the court erroneously declined even to consider whether the state tort law duty would "stand as an obstacle" to the effectiveness of federal drug regulation, mistakenly reading a provision in the FDCA as precluding this entire line of traditional preemption analysis. *Finally*, the court dismissed FDA's carefully considered judgment that tort suits like the instant one disrupt the agency's ability to ensure that the optimal information about the risks and benefits of using prescription drugs is provided to prescribers. Each of these conclusions was erroneous, and each independently warrants reversal.

I. The Court Should Grant Review To Correct Vermont's Rejection of Impossibility Conflict Preemption Stemming from its Mischaracterization of FDA's Comprehensive Regulatory Regime.

The Vermont Supreme Court's opinions in this case exemplify an ongoing dispute in the lower courts as to whether FDA's labeling approvals establish only a minimum requirement ("floor") for safety-related disclosures or, alternatively, a

calibrated approach ("floor and ceiling") that neither underwarns nor overdeters effective use. This base disagreement is very often outcome determinative and has been characterized by FDA as a threat to the integrity of its comprehensive regulatory regime. *See* 71 Fed. Reg. at 3934, App. 130a ("FDA has learned of several instances in which product liability lawsuits have directly threatened the agency's ability to regulate manufacturer dissemination of risk information for prescription drugs in accordance with the act.").

A majority of the Vermont Supreme Court adopted the former view in this case, following a line of cases holding that "FDA's drug labeling decisions impose only 'minimum' standards that are open to supplementation by state law through a jury's verdict enforcing a manufacturer's common law duty to warn." *Caraker v. Sandoz Pharm. Corp*, 172 F. Supp. 2d 1018, 1033 (S.D. Ill. 2001); *Mazur v. Merck & Co.*, 742 F. Supp. 239, 247 (E.D. Pa. 1990) ("Manufacturers must meet state safety requirements, whether codified or embodied in the common law, in addition to satisfying initial FDA requirements."); *Cartwright v. Pfizer, Inc.*, 369 F. Supp. 2d 876, 883 (E.D. Tex. 2005) ("FDA only sets forth minimum standards for labeling and safety of drugs."); *McNellis v. Pfizer, Inc.*, No. Civ. 05-1286, 2005 WL 3752269, at *7 (D.N.J. Dec. 29, 2005) ("FDA's regulations do not conflict with New Jersey's failure to warn law because those federal regulations merely set minimum standards with which manufacturers must comply."), *stay granted and motion to certify appeal granted*, No. Civ. 05-1286 (JBS), 2006 WL 2819046 (D.N.J. Sept. 29, 2006). Under this approach, state labeling requirements – whether imposed through positive legislative enactments or judicial decree – can almost never be incompatible with FDA's labeling regime. App. 15a ("When further warnings become necessary, the manufacturer is at least partially responsible for taking additional action, and if it fails to do so, it cannot rely on the FDA's continued approval of its labels as a shield against state tort liability.").

Chief Justice Reiber's dissent looked to different authority holding that "inadequate warning claim[s] would . . . conflict

with the federal requirements imposed during the regulation of the prescription drug by, "in effect, allowing a state regulation to impose labeling requirements contrary to those required by federal law." *Needleman v. Pfizer, Inc.*, No. 3:03-CV-3073-N, 2004 WL 1773697, at *2 (N.D. Tex. Aug. 6, 2004); *In re Bextra & Celebrex Marketing Sales Practices & Prod. Liab. Litig.*, No. 05-1699, 2006 WL 2374742, at *10 (N.D. Cal. Aug. 16, 2006) ("Plaintiffs' state law failure-to-warn-claims conflict with the FDA's determination of the proper warning and pose an obstacle to the full accomplishment of the objectives of the FDCA."); *Ehlis v. Shire Richwood, Inc.*, 233 F. Supp. 2d 1189, 1198 (D.N.D. 2002) (finding that prescription drug warning claim was preempted where "FDA dictates the contents of the label" and where "defendants were prohibited from changing it without prior approval from the FDA, except in limited circumstances for a limited period of time"), *aff'd*, 367 F.3d 1013 (8th Cir. 2004).

As Chief Justice Reiber explained, it would have been literally impossible for Wyeth to have complied with both the duty newly imposed under Vermont common law and FDA's command that Phenergan be marketed under labeling identical to that submitted by Wyeth on May 8, 1998. Respondent's cause of action originated from – and this case ultimately turned on – the premise that Phenergan's labeling should have foreclosed IV push administration of Phenergan. App. 37a ("[W]hat plaintiff sought was an elimination of a use of Phenergan that had been approved by the FDA.") (Reiber, C.J., dissenting). Thus, Wyeth could have complied with the legal duty it allegedly breached under Vermont law only if it had modified its FDA-approved label without prior FDA authorization before April 7, 2000, when Respondent was injected. Unless federal law permitted such modification, well-established conflict preemption principles would preclude holding Wyeth liable for failing to follow a state mandate that would have forced it to violate federal law. *See Freightliner Corp. v. Myrick*, 514 U.S. 280, 287 (1995).

No FDCA provision authorizes manufacturers to modify FDA-approved labeling without prior FDA consent. Indeed, as the Vermont Supreme Court acknowledged, the FDCA conditions the right to ship prescription drugs in interstate commerce on the use of FDA-approved labeling. As FDA routinely advises manufacturers receiving New Drug approvals, "[m]arketing the product with [labeling] that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug." *Letter from Edward Cox, Acting Director, Center for Drug Evaluation and Research, to David Hallinan, VP Regulatory Affairs, Idenix Pharms., Inc.* (Oct. 25, 2006), *available at* http://www.fda.gov/cder/foi/appletter/2006/022011 5000ltr.pdf (approving NDA 22-011 (Tyzeka)); *see also* App. 165a (commanding that Phenergan's "final printed labeling . . . must be identical to the [FDA-approved] draft package insert"). Marketing a misbranded or unapproved prescription drug would subject the manufacturer to substantial criminal and civil penalties. 21 U.S.C. §§ 332(a), 333(a), 334.

To meet the need to disseminate newly discovered safety information without delay, FDA adopted its "change being effected," or "CBE," regulation, 21 C.F.R. § 314.70(c)(6)(iii), in 1982. Rather than properly interpreting that regulation as a limited exception to FDCA's pre-approval labeling regime, however, courts adopting the "minimum" standards approach have seized on it to open the door to far-reaching state safety regulation. The CBE regulation describes certain categories of interim labeling changes that manufacturers may make without prior FDA approval, including "[t]o add or strengthen an instruction about dosage or administration that is intended to increase the safe use of the drug product." *Id.* § 314.70(c)(6)(iii)(C). Under the Vermont court's construction, this regulation allows "unilateral changes to drug labels whenever the manufacturer believes it will make the product safer, and places no limit on the duration of pre-approval warnings unless the FDA disapproves of the change." App. 13a (citation omitted); *see also Caraker*, 172 F. Supp. 2d at 1034 ("Even after approval, additional or more forceful warnings may,

in the drug manufacturer's judgment, be added to labeling *without prior FDA approval* and on the drug manufacturers' own initiative."). Thus, "[w]hile specific federal labeling requirements and state common-law duties might otherwise leave drug manufacturers with conflicting obligations, § 314.70(c) allows manufacturers to avoid state failure-to-warn claims without violating federal law." App. 11a (citation omitted).

This expansive and result-oriented reading of the CBE regulation is clearly incompatible with FDA's overall regulatory labeling regime. As FDA explained in adopting the CBE provision in 1982, that regulation creates a limited exception to the general pre-approval regime to permit *newly discovered* information to be timely disseminated. *See* New Drug and Antibiotic Regulations, 47 Fed. Reg. 46,622, 46,623, 46,635 (Oct. 19, 1982) (codified at 21 C.F.R. pts. 310, 312, 314, 430, 431, 433); *see also Perry v. Novartis Pharma. Corp.*, 456 F. Supp. 2d 678, 682 (E.D. Pa. 2006) ("This particular regulation was promulgated precisely to allow drug-makers to quickly strengthen label warnings when evidence of *new* side effects are discovered." (emphasis added) (internal quotation marks and citation omitted)); *Weiss v. Fujisawa Pharm. Co.*, 464 F. Supp. 2d. 666, 675 (E.D. Ky. 2006) (explaining that a "drug manufacturer may warn patients and healthcare providers should they discover *new* evidence of a particular risk following the approval of the original label" (emphasis added)). While a "new information" trigger for using the CBE provision is not express in its text, it is necessarily implicit in FDA's larger regulatory scheme. *See* Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,447 (June 26, 1979) (codified at 21 C.F.R. pts. 201-202); 71 Fed. Reg. at 3934, App. 128a-132a. FDA's comprehensive, particularized regulation of label formats and wording at the time of NDA approval cannot be reconciled with according manufacturers thereafter an unlimited ability to modify critical label language without prior FDA approval. *See Smith v. United States*, 508 U.S. 223, 234 (1993) ("A provision . . . is often clarified by the remainder of the statutory scheme . . .

because only one of the permissible meanings produces a substantive effect that is compatible with the rest of the law." (internal quotation marks and citation omitted)). In the words of Chief Justice Reiber, "the regulation does not allow manufacturers to simply reassess and draw different conclusions regarding the same risks and benefits already balanced by the FDA." App. 40a.

The facts of this case clearly show how the FDA regime can be disrupted by the CBE minimum standards approach. Here, the record unequivocally established that all information relating to the risks of IV injection of Phenergan put before the jury was available to FDA when it acted on Wyeth's supplemental NDA in 1997. The Vermont judicial process simply differed with FDA on the risk-benefit assessment appropriate to these facts, thus turning the CBE regulation into a recipe for balkanized and unbounded state second-guessing of federal regulatory actions. *See* App. 65a (calling FDA's regulatory process "slow and imperfect" and suggesting that FDA did not review "intravenous administration of Phenergan with scientific rigor or any sense of urgency").

This Court and the federal courts of appeal consistently have made clear that Congress has safeguarded FDA's science-based discretionary decisions from second-guessing in the federal courts, let alone fifty state courts. *See, e.g.*, *Heckler v. Chaney*, 470 U.S. 821, 835 (1985); *see also Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 653-54 (1973) ("The determination whether a drug is generally recognized as safe and effective . . . necessarily implicates complex chemical and pharmacological considerations" and is "peculiarly suited to initial determination by the FDA."); *Nutraceutical Corp. v. Von Eschenbach*, 459 F.3d 1033, 1043 (10th Cir. 2006) ("The review of scientific literature is properly in the province of the FDA, to which this Court grants deference based on its expertise."); *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995) ("[FDA's] judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us.").

Distorting the CBE regulation to permit second-guessing by judges and juries in prescription drug injury cases, as occurred here,

is particularly pernicious. While FDA makes risk-benefit labeling decisions from a systemic, forward-looking perspective to optimize use of beneficial treatments, *supra* at 4, state judicial decisions make the same determinations "in hindsight through the lens of a single catastrophic case," App. 62a, and with an inevitable bias toward finding fault as a basis for compensation. Were manufacturers to label in response to, or in anticipation of, state determinations, they would be subject to myriad conflicting mandates, and numerous FDA judgments concerning optimal labeling and administrations of prescription drugs could be overridden, to the detriment of overall public health. *See Horn v. Thoratec Corp.*, 376 F.3d 163, 178 (3d Cir. 2004) (observing that excessive risk-oriented regulation "can harm the public health . . . by encouraging 'defensive labeling' by manufacturers to avoid state liability, resulting in scientifically unsubstantiated warnings and underutilization of beneficial treatments").

This Court should grant review to restore the integrity of FDA's regulatory regime in a "case in which the Federal Government has weighed the competing interests relevant to the particular requirement in question, reached an unambiguous conclusion about how those competing considerations should be resolved in a particular case or set of cases, and implemented that conclusion via a specific mandate on manufacturers or producers." *Medtronic Inc. v. Lohr*, 518 U.S. 470, 501 (1996). At least absent newly discovered scientific information permitting action under section 314.70(a), manufacturers like Wyeth should not be held liable for adhering to an FDA-approved label.

II. The Court Should Grant Review To Clarify the Effect, If Any, of the Presumption Against Preemption and Section 202 of the 1962 FDCA Amendments on the Application of "Obstacle" Conflict Preemption to Prescription Drug Cases.

Review also would allow the Court to articulate the analytical framework for applying conflict preemption principles

to the prescription drug regime when FDA's labeling regime permits manufacturers to initiate some modifications. Even if states have some authority to regulate such discretion as FDA affords to manufacturers, well-established principles of preemption forbid states from exercising that authority in a manner that would obstruct the objectives of federal law. *See McDermott v. Wisconsin*, 228 U.S. 115, 132 (1913) ("[T]o the extent that state law interferes with or frustrates the operation of the acts of Congress, its provisions must yield to the superior Federal power. . . ."). This Court has consistently made clear that conflict preemption analysis requires consideration *both* of whether it would be impossible to comply with federal and state law *and* of whether the state law would stand as an obstacle to the objectives of federal law:

> The Court has not previously driven a legal wedge – only a terminological one – between "conflicts" that prevent or frustrate the accomplishment of a federal objective and "conflicts" that make it "impossible" for private parties to comply with both state and federal law. Rather, it has said that both forms of conflicting state law are "nullified" by the Supremacy Clause, and it has assumed that Congress would not want either kind of conflict.

Geier, 529 U.S. at 873 (citations omitted).

The Vermont Supreme Court majority, however, simply declined to analyze obstacle preemption. The court determined that this line of inquiry was foreclosed by section 202 of the 1962 amendments to the FDCA, which it read as limiting the operation of preemption to cases in which it is *impossible* for a manufacturer to comply with both state and federal law. App. 22a ("[U]nder any circumstances where it is possible to comply with both state law and the FDCA, the state law in question is consistent with the purposes and objectives of Congress."). The majority attempted to bolster its conclusion by relying on a "presumption against preemption" of state regulatory powers in the area of public health. App. 23a-24a.

The majority's construction of section 202's "direct and positive" language is mistaken. This Court has made clear that the existence of such savings clauses specifically designed to protect the operation of state law does not preclude application of conflict preemption – including obstacle preemption. *See Geier*, 529 U.S. at 873-74 ("The Court has thus refused to read general "saving" provisions to tolerate actual conflict *both* in cases involving impossibility *and* in frustration-of-purpose cases. . . ." (internal quotation marks and citations omitted)). Instead of foreclosing conflict preemption, such provisions – within an otherwise comprehensive regulatory scheme – are best read to indicate Congress's intent merely to preclude field preemption – on which Wyeth does not rely. *See Schneidewind v. ANR Pipeline Co.*, 485 U.S. 293, 299-300 (1988).

That is precisely the effect of section 202. Because the 1962 FDCA amendments greatly expanded FDA's regulatory authority, there was legitimate concern that Congress might have been deemed to occupy the field of drug safety. The use of the phrase "direct and positive" was intended to preclude field preemption while fully preserving conflict preemption, nothing more. As the House sponsor of section 202 explained, this provision "would merely say that this Food and Drug Act shall not be construed as the intent of Congress to abolish *all State laws on the same subject where they are not in conflict with the Federal law.*" *See* 108 Cong. Rec. 21,083 (1962) (statement of Rep. Smith) (emphasis added). Indeed, courts determining whether a "direct and positive" conflict exists routinely conduct *both* an impossibility conflict *and* an obstacle conflict preemption analysis and make clear that this language operates only to bar field preemption. *See, e.g., Sinnot v. Davenport*, 63 U.S. (22 How.) 227, 242-43 (1859) (finding "direct and positive" conflict between federal and state law coasting trade provisions despite vessel owner's ability to comply with both and holding that "if this State law can be upheld, the full enjoyment of the right to carry on the coasting trade . . . is denied to the vessel in question"); *City of Camden v. Beretta U.S.A. Corp.*, 81 F. Supp. 2d 541, 549 (D.N.J. 2000) (finding that Gun Control Act's

"direct and positive conflict" phrase "compels a finding that the Gun Control Act only may be raised as an ordinary preemption defense to a conflicting state law, and not as a jurisdictional bar to all state claims relating to firearms" (internal quotation marks omitted)).[6]

The general presumption against preemption does not alter this result. The presumption is designed to ensure that "the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947). Importantly, however, this presumption "is not triggered when the State regulates in an area where there has been a history of significant federal presence." *United States v. Locke*, 529 U.S. 89, 108 (2000); *see also Int'l Paper Co. v. Ouellette*, 479 U.S. 481, 491 (1987) ("[I]t is not necessary for a federal statute to provide explicitly that particular state laws are pre-empted."). In this regard, FDA has observed that "[i]n determining the proper role for state law in this context, . . . it is significant that the federal government has been regulating the manufacture and sale of drugs since 1906" – *i.e.*, for more than a century. Br. of the United States as Amicus Curiae in Support of Defendants-Appellees (filed Dec. 4, 2006), *Colacicco v. Apotex, Inc.*, No. 06-3107 (3d Cir.), at 17-18 n.7 ("Colacicco Br."). Granting review would enable this Court to make clear that state courts are not free simply to ignore this Court's settled "obstacle" conflict preemption doctrine through the overzealous application either of "direct and positive conflict" provisions or of the presumption against preemption.

The Vermont court should have examined whether the common law duty imposed on Wyeth posed an obstacle to FDA's

[6] This Court also has made clear that a federal statute's use of the term "provision" refers to positive enactments – not tort suit judgments. *See Cippollone v. Liggett Group, Inc.*, 505 U.S. 504, 518 (1992); *see also* Black's Law Dictionary 1262 (8th ed. 2004) (defining "provision" as "[a] clause in a statute, contract, or other legal instrument"). By its express terms, section 202 thus would not bar obstacle preemption even under the Vermont majority's misconstruction.

accomplishment of its congressionally mandated regulatory objectives. Under that analysis, the jury's verdict is preempted. As explained *supra* at 3, Congress specifically charged FDA with optimizing the use of prescription drugs by balancing their risks against their benefits to the overall public health. Permitting state tribunals to impose differing risk-benefit judgments on manufacturers, and to coerce labeling changes that FDA would not accept, would defeat congressional intent and lead to conflicting safety and warning standards imposed through the backward-looking lens of individual claims instead of the forward-looking public health determination that Congress mandated.

The facts of this case demonstrate why a state court's backward-looking, case-specific focus is inconsistent with FDA's broader regulatory perspective. FDA evaluated the risks associated with IV injection of Phenergan over a period of decades. Based on its scientific expertise, FDA determined that the efficacy benefits outweighed the risks and that physicians should retain the option to administer Phenergan via IV push, taking account of the extensive precautions and warnings in the approved label. App. 167a. FDA's determinations reflect its considered judgment that Phenergan's label reflected the correct risk-benefit balance and thus would render the drug of greatest benefit to the greatest number of people. *See United States v. Rutherford*, 442 U.S. 544, 555 (1979) ("[FDA] generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use."). The Vermont Supreme Court would allow a jury to disagree with FDA's risk-benefit assessment and to override the federal regime by imposing a different labeling regime on Wyeth.

This is a paradigmatic case of state law frustrating the objectives and purposes of a federal regulatory regime by foreclosing a treatment option that the federal government has decided to hold open. As this Court made clear in *Geier*, such interference cannot survive constitutional scrutiny. In *Geier*, this Court held that a state common law duty to install airbags in all cars was preempted where federal regulation "deliberately

provided the manufacturer with a range of choices among different passive restraint devices." 529 U.S. at 875. *Geier* held that the state duty "would have presented an obstacle to the variety and mix of devices that the federal regulation sought" and "stood as an obstacle to the general passive restraint phase-in that the federal regulation deliberately imposed." *Id.* at 881; *see also Int'l Paper Co.*, 479 U.S. at 494 (striking down state law under conflict preemption that "upset[] the balance of public and private interests so carefully addressed by the [federal] Act"); *Buckman Co. v. Pls.' Legal Comm.*, 531 U.S. 341, 348 (2001) (observing that FDA uses its authority "to achieve a somewhat delicate balance of statutory objectives" and that this balance "can be skewed by allowing" state tort law claims that second-guess FDA's enforcement decisions).

Just as the petitioner in *Geier* could not use tort law to foreclose choices that the Department of Transportation deemed appropriate, Vermont here cannot be permitted to disturb the hierarchy of options for Phenergan administration that FDA repeatedly chose to preserve in Phenergan's labeling. This Court should grant certiorari and reverse the decision below so that lower courts will undertake the careful review necessary to determine whether compliance with a state-enforced duty, even if not expressly foreclosed by federal command, would, as here, obstruct rather than complement the objectives and purposes of FDA regulation.[7]

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[7] *Bates v. Dow Agrosciences LLC*, 544 U.S. 431 (2005), is fully consistent with this understanding. In *Bates*, this Court held that federal law did not expressly preempt "parallel" state law remedies for violation of federal misbranding law. *See* 544 U.S. at 449-51. Here, unlike *Bates*, Vermont common law seeks to provide litigants a cause of action separate and distinct from federal law; indeed, the Vermont courts made clear that Wyeth would be held liable irrespective of its fidelity to the federal labeling mandate. App. 28a. Accordingly, the reasoning that saved state "parallel requirements" from preemption is wholly inapposite here. The Vermont common law rule and FDA's labeling regime are not parallel.

III. The Court Should Grant Review To Resolve the Conflict Concerning the Degree of Deference that Courts Should Accord FDA's Formal Position on the Extent to Which State Tort Law Labeling Judgments Interfere with FDA's Labeling Regime.

Finally, this Court should grant review to resolve a lower court split on whether FDA's recently expressed judgments with respect to the adverse impact of state tort suits on its comprehensive prescription drug labeling regime are entitled to deference. In its preamble to an amended labeling regulation, FDA recently reiterated its longstanding view that suits such as this one obstruct its ability to ensure that prescribers receive accurate and helpful information about the proper uses of prescription drugs. *See* 71 Fed. Reg. at 3935, App. 132a-133a. The agency has explained why, in its expert judgment, additional labeling requirements imposed by state law may interfere with its ability to carry out its congressionally mandated function:

> State law actions . . . threaten FDA's statutorily prescribed role as the expert Federal agency responsible for evaluating and regulating drugs. State actions are not characterized by centralized expert evaluation of drug regulatory issues. Instead, they encourage, and in fact require, lay judges and juries to second-guess the assessment of benefits versus risks of a specific drug to the general public – the central role of FDA – sometimes on behalf of a single individual or group of individuals. That individualized reevaluation of the benefits and risks of a product can result in relief – including the threat of significant damage awards or penalties – that creates pressure on manufacturers to attempt to add warnings that FDA has neither approved nor found to be scientifically required. This could encourage manufacturers to propose "defensive labeling" to avoid State liability, which, if implemented,

> could result in scientifically unsubstantiated warnings and underutilization of beneficial treatments.

Id. at 3935.

This observation, based on FDA's expertise and experience, fully supports FDA's view that "[s]tate law conflicts with and stands as an obstacle to achievement of the full objectives and purposes of Federal law if it purports to preclude a firm from including in labeling . . . a statement that is included in [FDA-approved] prescription drug labeling." *Id.*; *see also id.* at 3934 ("FDA approval of labeling under the act, whether it be in the old or new format, preempts conflicting or contrary State law."). For all these reasons, FDA reiterated that it "interprets the act to establish both a 'floor' and a 'ceiling,' such that additional disclosures of risk information can expose a manufacturer to liability under the act if the additional statement is unsubstantiated or otherwise false or misleading." *Id.* at 3935.[8]

FDA expressed this same view in a number of recent amicus briefs. *See, e.g.*, Colacicco Br., *supra*; Letter Br. for FDA (filed Sept. 21, 2006), *Perry v. Novartis Pharms.*, No. 05-5350 (E.D. Pa.) ("Perry Br."). FDA explained therein that, "[i]n that context of drug labeling, Congress has authorized FDA to use scientific expertise to determine, in the first instance, what warnings are appropriate and necessary for a particular drug." Colacicco Br., *supra*, at 20. Moreover, "[i]f the agency had made a determination at a relevant time that a particular warning was unsubstantiated or would otherwise render the drug misbranded, then federal preemption bars liability for the failure to provide that warning." *Id.* at 23 n.10. Accordingly, "[e]ven if compliance with both state and federal law in these circumstances would not be impossible, state tort liability would pose a sufficient

[8] *See Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 718 (1985) (confirming that agencies "can speak through a variety of means, including regulations, preambles, interpretive statements, and responses to comments"); *Fid. Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 158 (1982) (looking to regulatory preamble "for the administrative construction of the regulation, to which 'deference is . . . clearly in order'" (quoting *Udall v. Tallman*, 380 U.S. 1, 16 (1965)).

threat to federal regulatory objectives to be preempted under the Supremacy Clause." Perry Br., *supra*, at 10.[9]

According to the Vermont Supreme Court, "FDA's statement is neither an authoritative interpretation of an ambiguous statutory provision entitled to deference, nor a persuasive policy statement entitled to respect." App. 28a (internal citations omitted); *see also Jackson v. Pfizer, Inc.*, 432 F. Supp. 2d 964, 968 (D. Neb. 2006) ("The recent notice issued by the FDA claiming preemption is not persuasive."). In particular, the majority refused to credit FDA's conclusion that the "direct and positive" language of section 202 did not foreclose an analysis of state law interference with FDA's regulatory objectives. App. 135a, 21a.

Other courts have taken a different view of the importance of FDA's views on how state tort suits conflict with its regulatory regime and hamper its ability to do its job. *See In re Bextra*, 2006 WL 2374742, *6 ("The FDA's interpretation of the preemptive effect of its regulations is entitled to deference."); *Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514, 525 (E.D. Pa. 2006) ("The FDA's view is critical to this Court's analysis because Supreme Court precedent dictates that an agency's interpretation of the statute and regulations it administers is entitled to deference."); *see also Horn*, 376 F.3d at 171 ("[T]he Supreme Court has instructed us that the FDA's preemption determinations are significant and should inform our interpretation . . . .").

This latter view is correct – FDA's substantive interpretation of its own regulations should be entitled to considerable deference – not the dismissive treatment given by the Vermont Supreme Court. *See Auer v. Robbins*, 519 U.S. 452, 461 (1997)

[9] *See Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 883 (2000) (granting deference to the views expressed in an amicus brief submitted by the Solicitor General); *Auer v. Robbins*, 519 U.S. 452, 453 (1997) ("The Secretary's interpretation is not rendered unworthy of deference by the fact that it is set forth in an *amicus* brief; it is not a position adopted in response to litigation, and there is no reason to suspect that it does not reflect the Secretary's fair and considered judgment.").

(holding that an agency's interpretation of its regulations is "controlling unless plainly erroneous or inconsistent with the regulation" (internal quotation marks and citation omitted)). Similarly, FDA is best able to determine what interferes with its ability to fulfill its statutory mandate, and its views on that issue also merit substantial deference:

> Congress has delegated to [the agency] authority to implement the statute; the subject matter is technical; and the relevant history and background are complex and extensive. The agency is likely to have a thorough understanding of its own regulation and its objectives and is "uniquely qualified" to comprehend the likely impact of state requirements.

Geier, 529 U.S. at 883; *see also Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994) (finding that deference is especially warranted where agency decisions "require significant expertise and entail the exercise of judgment grounded in policy concerns" (internal quotation marks and citation omitted)).

Prescription drug labeling is precisely the type of complex and technical regulatory regime that warrants deference to the expertise of the agency that Congress charged with administering it. *See Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 455 (2005) ("As suggested by *Medtronic*, the federal agency charged with administering the statute is often better able than are courts to determine the extent to which state liability rules mirror or distort federal requirements.") (Breyer, J., concurring). By disregarding FDA's interpretation of its own regulations and its views on the impact of state tort suits on the agency's regulatory objectives, the Vermont court committed a crucial error that infected its entire preemption analysis. The Court should grant review to correct this error and resolve this split in authority.

CONCLUSION

For the foregoing reasons, this Court should grant the petition for a writ of certiorari.

Respectfully submitted,

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APPENDIX

APPENDIX A — OPINION OF THE VERMONT SUPREME COURT FILED OCTOBER 27, 2006

SUPREME COURT

No. 2004-384

Diana Levine

v.

Wyeth

On Appeal from
Washington Superior Court

October Term, 2005

Geoffrey W. Crawford, J.

Richard I. Rubin and Kerry B. DeWolfe of Rubin, Kidney, Myer & DeWolfe, Barre, for Plaintiff-Appellee.

Allan R. Keyes and R. Joseph O'Rourke of Ryan, Smith & Carbine, Ltd., Rutland, and Bert W. Rein, Karyn K. Ablin and Sarah E. Botha of Wiley Rein & Fielding LLP, and Daniel S. Pariser of Arnold & Porter LLP, Washington, D.C., for Defendant-Appellant.

Present: REIBER, C.J., DOOLEY and JOHNSON, JJ., and MORRIS, D.J., and ALLEN, C.J. (Ret.), Specially Assigned.

Appendix A

JOHNSON, J.

Defendant Wyeth, a drug manufacturer, appeals from a jury verdict in favor of plaintiff Diana Levine, who suffered severe injury and the amputation of her arm as a result of being injected with defendant's drug Phenergan. Plaintiff claimed at trial that defendant was negligent and failed to provide adequate warnings of the known dangers of injecting Phenergan directly into a patient's vein. Defendant argues that the trial court should not have allowed the jury to consider plaintiff's claims because the claims conflict with defendant's obligations under federal law regulating prescription drug labels. We hold that there is no conflict between state and federal law that requires preemption of plaintiff's claim. Defendant also raises two claims of error relating to the jury instructions on damages. We hold that the court's rulings on these jury instructions were correct, and we affirm.

In April 2000, plaintiff was injected with defendant's drug Phenergan at Northeast Washington County Community Health, Inc. ("the Health Center"). The drug was administered to treat plaintiff's nausea resulting from a migraine headache. Plaintiff received two injections. The drug was first administered by intramuscular injection. Later the same day, when plaintiff's nausea continued, she received a second dose by a direct intravenous injection into her arm, using a procedure known as "IV push." The second injection resulted in an inadvertent injection of Phenergan into an artery. As a result, the artery was severely damaged, causing gangrene. After several weeks of deterioration, plaintiff's hand and forearm were amputated.

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Plaintiff brought a superior court action for negligence and failure-to-warn product liability, alleging that defendant's inadequate warning of the known dangers of direct intravenous injection of Phenergan caused her injuries. During a five-day jury trial, both parties presented expert testimony regarding the adequacy of the warnings defendant placed on Phenergan's label. Plaintiff's experts testified that the label should not have allowed IV push as a means of administration, as it was safer to use other available options, such as intramuscular injection or administration through the tubing of a hanging IV bag. Defendant's expert testified that allowing IV push with instructions cautioning against inadvertent arterial injection was sufficient. The court instructed the jurors that they could consider the FDA's approval of the label in use at the time of plaintiff's injury, but that the label's compliance with FDA requirements did not establish the adequacy of the warning or prevent defendant from adding to or strengthening the warning on the label. At the conclusion of the trial, the jury found in favor of plaintiff on both the negligence and product-liability claims and awarded her $2.4 million in economic damages and $5 million in non-economic damages. Pursuant to the parties' stipulation, this award was reduced to a total of $6,774,000 to account for pre-judgment interest and plaintiff's recovery in a settlement of a separate action she had filed against the Health Center.

In a summary judgment motion prior to trial, as well as in its timely motion for judgment as a matter of law following trial, both of which the superior court denied, defendant argued that federal law preempted plaintiff's claim. These arguments rested in part on defendant's contention that it

had submitted an adequate warning to the FDA, but that the FDA rejectedthe change because it did not favor strengthening the warning.[1] Plaintiff contended that neither warning would have been adequate. The trial court stated, in

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1. The warning on the label that was in use in 2000 read in relevant part:

INADVERTENT INTRA-ARTERIAL INJECTION: Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injection of [Phenergan], usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances. Intravenous injection was intended in all the cases reported but perivascular extravasation or arterial placement of the needle is now suspect. There is no proven successful managemert of this condition after it occurs. . . .

When used intravenously [Phenergan] should be given in a concentration no greater than 25 mg per ml and at a rate not to exceed 25 mg per minute. WHEN ADMINISTERING ANY IRRITANT DRUG INTRAVENOUSLY IT IS USUALLY PREFERABLE TO INJECT IT THROUGH THE TUBING OF AN INTRAVENOUS INFUSION SET THAT IS KNOWN TO BE FUNCTIONING SATISFACTORILY.

(Emphasis added.) The revised warning the FDA failed to adopt read in relevant part:

INADVERTENT INTRA-ARTERIAL INJECTION: There are reports of necrosis leading to gangrene, requiring amputation, (Cont'd)

its decision on defendant's motion for judgment as a matter of law, that although the FDA had rejected a new warning, the agency's "brief comment" failed to explain its reasoning or demonstrate that it "gave more than passing attention to the issue of whether to use an IV infusion to administer the drug. The proposed labeling change did not address the use of a free-flowing IV bag." The court concluded that there was "no basis for federal preemption" and upheld the jury's verdict.

Defendant claims the superior court erred by: (1) failing to dismiss plaintiff's claim on the basis that the Food and Drug Administration's approval of the Phenergan label

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(Cont'd)
following injection of [Phenergan], usually in conjunction with other drugs; the intravenous route was intended in these cases, but arterial or partial arterial placement of the needle is now suspect. . . .

There is no established treatment other than prevention:

1. Beware of the close proximity of arteries and veins at commonly used injection sites and consider the possibility of aberrant arteries.

2. When used intravenously, [Phenergan] should be given in a concentration no greater than 25 mg/ml and a rate not to exceed 25 mg/minute. INJECTION THROUGH A PROPERLY RUNNING INTRAVENOUS INFUSION MAY ENHANCE THE POSSIBILITY OF DETECTING ARTERIAL PLACEMENT. IN ADDITION, THIS RESULTS IN DELIVERY OF A LOWER CONCENTRATION OF ANY ARTERIOLAR IRRITANT.

(Emphasis added.)

preempted state common law claims that the label was inadequate; (2) failing to instruct the jury to reduce plaintiff's damages by the amount of fault attributable to the Health Center; and (3) failing to instruct the jury to calculate the present value of plaintiff's damages for future non-economic losses. We reject these claims of error, and we affirm.

I. Federal Preemption

Defendant's principal argument on appeal is that the court should have dismissed plaintiff's claim because it was preempted by federal law. Defendant asserts that any state common law duty to provide a stronger warning about the dangers of administering Phenergan by IV push conflicts with the FDA's approval of the drug's label. As preemption is a question of law, we review the trial court's decision de novo. *Office of Child Support v. Sholan*, 172 Vt. 619, 620, 782 A.2d 1199, 1202 (2001) (mem.). We hold that the jury's verdict against defendant did not conflict with the FDA's labeling requirements for Phenergan because defendant could have warned against IV-push administration without prior FDA approval, and because federal labeling requirements create a floor, not a ceiling, for state regulation.

The United States Constitution provides that federal law is the supreme law of the land. U.S. Const. art. VI, cl. 2. The Supremacy Clause is the basis for the doctrine of preemption, according to which "state law that conflicts with federal law is 'without effect.'" *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516, 112 S.Ct. 2608, 120 L.Ed.2d 407 (1992) (quoting *Maryland v. Louisiana*, 451 U.S. 725, 746, 101 S.Ct. 2114, 68 L.Ed.2d 576 (1981)). In Cipollone, the Court

described the relevant analysis for determining whether Congress intended a federal statute to preempt state law:

> Congress' intent may be explicitly stated in the statute's language or implicitly contained in its structure and purpose. In the absence of an express congressional command, state law is pre-empted if that law actually conflicts with federal law, or if federal law so thoroughly occupies a legislative field as to make reasonable the inference that Congress left no room for the States to supplement it.

Id. (quotations and citations omitted). Absent clear congressional intent to supersede state law, including state common law duties, there is a presumption against preemption. *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485, 116 S.Ct. 2240, 135 L.Ed.2d 700 (1996) ("[B]ecause the States are independent sovereigns in our federal system, we have long presumed that Congress does not cavalierly pre-empt state-law causes of action."); *Cipollone*, 505 U.S. at 516 ("Consideration of issues arising under the Supremacy Clause 'start[s] with the assumption that the historic police powers of the States [are] not to be superseded by ... Federal Act unless that [is] the clear and manifest purpose of Congress.'" (quoting *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230, 67 S.Ct. 1146, 91 L.Ed. 1447 (1947))). This presumption has "add[ed] force" when there has been a "long history of tort litigation" in the area of state common law at issue. *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449, 125 S.Ct. 1788, 161 L.Ed.2d 687 (2005).

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Defendant concedes that Congress has not expressly preempted state tort actions through the Food, Drug and Cosmetics Act (FDCA), 21 U.S.C. ¶ ¶ 301-399, and that Congress did not intend the FDCA to occupy the entire field of prescription drug regulation. Rather, it asserts that plaintiff's action "actually conflicts with federal law." *Cipollone*, 505 U.S. at 516. This requires defendant to show either that "it is impossible for a private party to comply with both state and federal requirements," or that Vermont's common law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Freightliner Corp. v. Myrick*, 514 U.S. 280, 287, 115 S.Ct. 1483, 131 L.Ed.2d 385 (1995) (quotations and citations omitted).

Defendant presents two alternative bases for its assertion of conflict preemption: (1) in the specific context of the Phenergan label, the FDA was aware of the dangers of IV-push administration and specifically ordered defendant to use the warning it used, making it impossible for defendant to comply with both its state common-law duty and the requirements of federal law; and (2) by penalizing drug companies for using FDA-approved wording on drug labels, state tort claims like plaintiff's present an obstacle to the purpose of the FDA's labeling regulations. Before reaching these issues, we briefly examine the FDA's role in regulating prescription drug labels and the general approach courts have taken to the preemptive effect of federal labeling requirements.

Appendix A

A. Regulatory Background

Prior to distributing a prescription drug such as Phenergan, the manufacturer must submit a New Drug Application (NDA) for FDA approval. 21 U.S.C. ¶ 355(a). The FDA must approve the application unless it fails to meet certain criteria, including whether test results and other information establish that the drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof," whether there is "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof," and whether, "based on a fair evaluation of all material facts, such labeling is false or misleading in any particular." *Id.* ¶ 355(d).

"FDA regulations mandate the general format and content of all sections of labels for all prescription drugs as well as the risk information each section must contain," and "[f]inal approval of the NDA is 'conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed label prior to marketing.'" *McNellis v. Pfizer, Inc.*, 2005 WL 3752269, at *4 (D.N.J.) (citing 21 C.F.R. ¶¶ 201.56, 201.57, and quoting 21 C.F.R. 314.105(b)). Once a drug and its label have been approved, any changes to the label ordinarily require submission and FDA approval of a "Supplemental NDA." *Id.*; 21 C.F.R. 314.70(b)(2)(v)(A).

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If the NDA process and the submission of changes for FDA approval were the exclusive means of creating and altering prescription drug labels, this might be a very different case. A key FDA regulation, however, allows a drug's manufacturer to alter the drug's label without prior FDA approval when necessary. The regulation provides in relevant part:

> (6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:
>
> . . . .
>
> (iii) Changes in the labeling ... to accomplish any of the following:
>
> (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;
>
> . . . .
>
> (B) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product[.]

21 C.F.R. ¶ 314.70(c).

Appendix A

Section 314.70(c) creates a specific procedure allowing drug manufacturers to change labels that are insufficient to protect consumers, despite their approval by the FDA. "The FDA's approved label ... can therefore be said to set the minimum labeling requirement, and not necessarily the ultimate label where a manufacturer improves the label to promote greater safety." *McNellis*, 2005 WL 3752269, at *5. While specific federal labeling requirements and state common-law duties might otherwise leave drug manufacturers with conflicting obligations, ¶ 314.70(c) allows manufacturers to avoid state failure-to-warn claims without violating federal law. *Id.* ("[I]t is apparent that prior FDA approval need not be obtained, nor will a product be deemed mislabeled, if the manufacturer voluntarily or even unilaterally strengthens the approved warnings, precautions or potential adverse reactions upon the label pursuant to 21 C.F.R. ¶ 314.70(c)(6)(iii)(A)."). There is thus no conflict between federal labeling requirements and state failure-to-warn claims. Section 314.70(c) allows, and arguably encourages, manufacturers to add and strengthen warnings that, despite FDA approval, are insufficient to protect consumers. State tort claims simply give these manufacturers a concrete incentive to take this action as quickly as possible.

B. Conflict Preemption in Other Jurisdictions

In light of the leeway created by ¶ 314.70(c) for drug manufacturers to add warnings, courts have been nearly unanimous in holding that state failure-to-warn tort claims do not conflict with federal law. See, e.g., *McNellis*, 2005 WL 3752269, at *7 ("[T]he FDCA and the FDA's regulations do not conflict with New Jersey's failure to warn law because

those federal regulations merely set minimum standards with which manufacturers must comply."). McNellis is the latest in a series of recent cases addressing this issue as it relates to the anti-depressant *Zoloft*, which allegedly increases the risk of suicide in some patients. See id., at *7-8 (denying summary judgment and rejecting conflict preemption in *Zoloft* case); accord *Zikis v. Pfizer, Inc.*, 2005 WL 1126909, at *2-3 (N.D.Ill.); *Witczak v. Pfizer, Inc.*, 377 F.Supp.2d 726, 729-30 (D.Minn.2005); *Motus v. Pfizer, Inc.*, 127 F.Supp.2d 1085, 1096-1100 (C.D.Cal.2000); *see also Cartwright v. Pfizer, Inc.*, 369 F.Supp.2d 876, 882 (E.D. Tex. 2005) ("With little exception, courts that have considered this exact issue have concluded that state failure to warn claims are not preempted by the FDCA and its attendant regulations."). *Contra Needleman v. Pfizer, Inc.*, 2004 WL 1773697, at *1 (N.D. Tex.) (granting summary judgment to the defendant on basis of conflict preemption).

The Zoloft cases are representative of a general rule that FDA approval of a drug's label does not preempt state failure-to-warn claims. See, e.g., *Eve v. Sandoz Pharm. Corp.*, 2002 WL 181972, at *1-3 (S.D.Ind.) (rejecting conflict preemption of failure-to-warn claim regarding the drug Parlodel); *Caraker v. Sandoz Pharm. Corp.*, 172 F.Supp.2d 1018, 1032 (S.D.Ill.2001) (same); *Bryant v. Hoffman-La Roche, Inc.*, 262 Ga.App. 401, 585 S.E.2d 723, 725 (Ga.Ct.App.2003) (heart medication); *Bell v. Lollar*, 791 N.E.2d 849, 854-55 (Ind.Ct.App.2003) (prescription pain medication); *Kurer v. Parke, Davis & Co.*, 2004 WI App 74, 21, 272 Wis.2d 390, 679 N.W.2d 867 (oral contraceptive). But see *Ehlis v. Shire Richwood, Inc.*, 233 F.Supp.2d 1189, 1198 (D.N.D.2002) (granting summary judgment to defendant on basis of conflict preemption of claim regarding the drug Adderall).

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Defendant cites two cases, Needleman and Ehlis, that support the preemptive effect of the FDCA in failure-to-warn cases regarding prescription drug labels. *Needleman*, 2004 WL 1773697, at *1; *Ehlis*, 233 F.Supp.2d at 1198. Needleman is not particularly helpful under the circumstances here. Its holding relied on the facts of the *Zoloft* litigation, particularly an FDA statement that the warning advocated by the plaintiff would have been misleading. 2004 WL 1773697, at *1. The courts in the other Zoloft cases took a different approach to the FDA's statement, in part because the FDA's statement was not "an official agency position," and in part because the FDA later retracted its position regarding the link between *Zoloft* and suicide. See, e.g., *Witczak*, 377 F.Supp.2d at 730. Here, the FDA has not indicated that a stronger warning would be misleading, so the reasoning of Needleman appears inapplicable to this case. Ehlis interpreted ¶ 314.70(c) as allowing unapproved changes to a label only temporarily, and only under "limited circumstances." 233 F.Supp.2d at 1197-98. We can find no support for this interpretation in the language of the regulation, which appears to allow unilateral changes to drug labels whenever the manufacturer believes it will make the product safer, and places no limit on the duration of pre-approval warnings unless the FDA disapproves of the change. 21 C.F.R. ¶ 314.70(c).

Defendant next attempts to draw a comparison to the regulation of medical devices under the FDCA, citing medical device cases in which state tort law has been preempted. See *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 348, 121 S.Ct. 1012, 148 L.Ed.2d 854 (2001) (holding that "fraud-on-the-FDA" claim relating to device regulated by Medical Device Amendments to FDCA was preempted); *Horn v.*

Thoratec Corp., 376 F.3d 163, 177 (3d Cir.2004) (holding that failure-to-warn claim was preempted by Medical Device Amendments). We find this analogy unpersuasive. Neither Buckman nor Horn weakens the force of the drug-labeling cases cited above. The claim that was preempted in Buckman was for "fraud on the FDA," not failure to warn; the Court held that the presumption against preemption applies only when a claim implicates "'the historic primacy of state regulation of health and safety,'" which is not the case when the claim arises from a federal statute. 531 U.S. at 347-48 (quoting *Medtronic*, 518 U.S. at 485). Plaintiff's negligence and product-liability claims fall squarely withn the scope of traditional state regulation, so it is appropriate to apply the presumption against preemption here. In Horn, the Third Circuit relied on an express preemption clause in the FDCA that relates only to medical devices. 376 F.3d at 176. Because no such clause exists for prescription drugs, Horn's reasoning does not apply to this case.

Finally, defendant cites a third group of cases relating generally to the United States Supreme Court's recent use of conflict preemption in other fields. This argument relies primarily on *Geier v. American Honda Motor Co.*, 529 U.S. 861, 120 S.Ct. 1913, 146 L.Ed.2d 914 (2000). In Geier, the Court held that state tort claims based on the production of automobiles without airbags conflicted with federal regulations making airbags one of several permissible safety equipment options. 529 U.S. at 881. Geier, however, rested on the conclusion that the Department of Transportation's intent in drafting the regulation at issue was to provide a range of different safety options, thus precluding any state determination that a specific type of equipment should be

required. *Id.* The history of the regulation at issue indicated that the agency intended to phase in automobile safety requirements gradually, allowing the public to choose between mandatory seatbelt laws at the state level and a federal passive-restraint requirement. *Id.* at 880-81. Allowing state tort claims based on the lack of a particular safety mechanism would have conflicted with both the agency's phase-in plan and its intent to provide consumers with a range of safety options. *Id.* at 881. The Court explicitly stated that in a different context, an agency could promulgate regulations that provided a floor, but not a ceiling, for state regulation. *Id.* at 870.

The FDA's labeling requirements are exactly that type of regulation. Section 314.70(c) does not allow us to interpret FDA approval of a drug label as anything but a first step in the process of warning consumers. When further warnings become necessary, the manufacturer is at least partially responsible for taking additional action, and if it fails to do so, it cannot rely on the FDA's continued approval of its labels as a shield against state tort liability. While a state common-law duty may encourage departure from a label that the FDA has approved in great detail, such a duty does not create a conflict with federal requirements because the FDA and the state share the purpose of encouraging pharmaceutical companies to alter their drug labels when they are inadequate to protect consumers. We agree with the significant majority of courts that state failure-to-warn claims are generally not preempted by federal labeling requirements.

We must now apply this reasoning to defendant's two original contentions: (1) notwithstanding the fact that it is generally possible for manufacturers to comply with both federal and state law through the procedures created by ¶ 314.70(c), the FDA's specific actions with respect to *Phenergan* made it impossible for defendant to comply with both federal and state law; and (2) even if plaintiff's claim and the cases cited above do not make it impossible for manufacturers to comply with both state and federal law, they present an obstacle to federal objectives.

C. Impossibility of Compliance

Defendant contends that in this case, it was impossible to comply with both state and federal law because the FDA prohibited the use of a stronger warning with respect to IV-push administration of Phenergan. This claim is not supported by the evidence defendant presented to the trial court. The record lacks any evidence that the FDA was concerned that a stronger warning was not supported by the facts, that such a stronger warning would distract doctors from other provisions in the drug's label, or that the warning might lead to less effective administration of the drug. Instead, defendant essentially relies on two factual assertions: 1) the FDA approved the label that was in use in 2000; and 2) the FDA, in reviewing the label for use in a different version of Phenergan, expressed its opinion of the adequacy of the warning in the original label by stating, "Retain verbiage in current label." AB 5, 5 n. 7

With respect to defendant's first assertion, our analysis above demonstrates that FDA approval of a particular label does not preempt a jury finding that the label provided insufficient warning, as defendant was free under ¶ 314.70(c) to strengthen the warning without prior FDA approval. Defendant's second assertion depends on the meaning of the instruction, "[r]etain verbiage in current label." Tort liability for defendant's failure to strengthen its warningcould have created a direct conflict requiring federal preemption only if the FDA intended the instruction to prohibit any language strengthening the original warning. In other words, unless we interpret the FDA's statement as evidence that it would have rejected any attempt by defendant to strengthen its label through ¶ 314.70(c), we cannot conclude that it was impossible for defendant to comply with its state common-law duty without violating federal law.

Defendant argues that the instruction reflected the FDA's opinion not only that a stronger warning was unnecessary, but also that it would have harmed patients by eliminating IV push as an option for administering *Phenergan*. The record does not support this interpretation. Defendant has provided a number of letters exchanged by the FDA and defendant regarding Phenergan's label, but these letters do not indicate the FDA's opinion of the value of IV-push administration. Neither the letters nor any other evidence presented to the jury indicated that the FDA wished to preserve the use of IV push as a method of administering Phenergan. Nor can we infer such concern from the agency's instruction to "[r]etain current verbiage" instead of adopting the proposed warning. The specific warning the agency rejected in favor of the original label did not indicate any more clearly than the

original label that IV-push administration was unsafe, which is what plaintiff argued made the original label inadequate. The FDA could have rejected the new warning for any number of reasons, including clarity or technical accuracy, without implicitly prohibiting a stronger warning. Defendant's unsupported hypothesis that the FDA saw the new warning as harmful seems among the least likely explanations, as the rejected proposal would not have eliminated IV push as an option for administering Phenergan.[2] With respect to IV administration, the original label read, "When administering any irritant drug intravenously it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily," while the proposed label stated, "[i]njection through a properly running intravenous infusion may enhance the possibility of detecting arterial placement. In addition, this results in delivery of a lower concentration of any arteriolar irritant." See supra 4 n. 1 (comparing proposed and original warnings). Simply stated, the proposed warning was different, but not stronger. It was

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2. The dissent appears to interpret any warning that would eliminate IV-push administration as inherently inconsistent with the FDA's approval of Phenergan for IV administration in general. We see no such inconsistency, as an approval of a drug for IV administration is not the same as a conclusion that all methods of IV administration are safe. In any case, a jury verdict in a failure-to-warn case simply establishes that the relevant warning was insufficient; it does not mandate a particular replacment warning. There may have been any number of ways for defendant to strengthen the Phenergan warning without completely eliminating IV-push administration. Our purpose in pointing out that the proposed warning the FDA rejected did not eliminate IV push is simply that rejecting this warning could not be seen as an affirmative effort by the FDA to preserve IV push as an option.

also no longer or more prominent than the original warning, so it could not have raised a concern that it might overshadow other warnings on the label or drive doctors away from prescribing the drug. There is no evidence that the FDA intended to prohibit defendant from strengthening the *Phenergan* label pursuant to ¶ 314.70(c).[3] Thus, we cannot conclude that it was impossible for defendant to comply with its obligations under both state and federal law.

D. Obstacle to Congressional Purposes and Objectives

Defendant next contends that state common-law liability for its use of an FDA-approved label presents an obstacle to federal objectives. We hold that plaintiff's claim does not interfere with any objective that can legitimately be ascribed to Congress. We agree with the reasoning in the cases cited above, supra 14-15, that federal labeling requirements pursuant to the FDCA create a floor, not a ceiling, for state regulation. Defendant presents a new FDA rule containing language disputing this reasoning, but this statement does not alter our conclusion that there is no conflict between federal objectives and Vermont common law.

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3. We also reject defendant's argument that it would have been prosecuted for "misbranding" if it had strengthened the label without prior approval. See *Witczak*, 377 F.Supp.2d at 731, 729 ("[T]he validity and authority of state law ... does not depend on speculative hypotheticals" regarding "assumptions of what the FDA would have done" in response to a stronger warning.).

Appendix A

1. The Purposes and Objectives of Congress

In the absence of a conflict that makes it impossible for a regulated entity to comply with both state and federal law, federal law will preempt state law only if it "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Freightliner*, 514 U.S. at 287 (quotations omitted). We must therefore examine what "the full purposes and objectives of Congress" were with respect to federal labeling requirements for prescription drugs. We agree with the McNellis court that a system under which "federal regulations merely set minimum standards with which manufacturers must comply" is

> fully consistent with Congress' primary goal in enacting the FDCA, which is "to protect consumers from dangerous products," *United States v. Sullivan*, 332 U.S. 689, 696, 68 S.Ct. 331, 92 L.Ed. 297 (1948), as well as Congress' stated intent that the FDCA "'must not weaken the existing laws,' but on the contrary 'it must strengthen and extend that law's protection of the consumer.'" *United States v. Dotterweich*, 320 U.S. 277[, 282] (1943) [quoting S.Rep. No. 152, 75th Cong., 1st Sess., p. 1].

2005 WL 3752269, at *7; *see also Witczak*, 377 F.Supp.2d at 731 ("Congress certainly did not intend to bar drug companies from protecting the public when enacting the FDCA; its goal was to protect the public.... Any contrary interpretation of Congress's intent is perverse.").

In fact, Congress has expressed its purposes clearly, not only in the general sense that the statute was intended to "protect the public," but also more specifically, with respect to the FDCA's preemptive effect. In the 1962 amendments to the FDCA, Congress included a clause expressly limiting the preemptive effect of the statute: "Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law ... unless there is a direct and positive conflict between such amendments and such provision of State law." Drug Amendments of 1962 (Harris Kefauver Act), Pub.L. No. 87 781, ¶ 202, 76 Stat. 780, 793 (1962).

This amendment essentially removes from our consideration the question of whether common-law tort claims present an obstacle to the purposes and objectives of Congress. Congress intended that the FDCA would leave state law in place except where it created a "direct and positive conflict" between state and federal law. Drug Amendments ¶ 202. This language "simply restates the principle that state law is superseded in cases of an actual conflict with federal law such that 'compliance with both federal and state regulations is a physical impossibility.'" See *S. Blasting Servs., Inc. v. Wilkes County*, 288 F.3d 584, 591 (4th Cir.2002) (interpreting "direct and positive conflict" language in the preemption clause of a federal statute governing explosive materials to allow states to "impose more stringent requirements than those contained in the federal regulations") (quoting *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 713, 105 S.Ct.

2371, 85 L.Ed.2d 714 (1985)).[4] In other words, under any circumstances where it is possible to comply with both state law and the FDCA, the state law in question is consistent with the purposes and objectives of Congress. Thus, our

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4. The debate surrounding the amendment helps confirm that it was intended to preserve the right of states to regulate beyond the federal requirements of the FDCA. During the floor debate in the House, the subject of preemption arose several times. First, Congressman Smith of California expressed concern that the bill, as reported, contained "no language ... which says anything to the effect that this particular measure will not preempt all State food and drug laws," and thus, might risk interfering with the efforts of some states to make their own, stricter regulations. 108 Cong. Rec. 21046 (1962) ("[I]t seems to me that if we are going to pass this law, someone ought to offer an amendment to make certain that the passage of this bill, which gives all of this power to the Department of Health, Education, and Welfare and the Food and Drug Administration, will not preempt any State laws"). Shortly thereafter, Congressman Harris of Arkansas, the primary House sponsor of the bill, offered his opinion that "there is nothing in this bill that in any way preempts the authority and prerogatives of the States." *Id.* at 21047. Congressman Schenck of Ohio agreed, stating, "[m]any very helpful State laws are in effect; many such laws in some instances are even stronger than Federal laws for the protection of human health in the public interest." *Id.* at 21056.

Congressmen Schenck and Harris, despite insisting that the bill as written would not preempt stronger state laws, eventually supported the "direct and positive conflict" amendment, and Schenck reiterated that preemption should not apply in the "many instances where State laws in the area of food and drugs and health are even stronger than some of the Federal laws." *Id.* at 21083. Neither the desirability of allowing states to regulate beyond the FDCA nor the intent of the amendment to protect such regulation from preemption was called into question during the debate.

discussion above regarding defendant's impossibility argument, supra 21-23, provides a complete answer to the question of preemption.

We recognize that our dissenting colleague has reached the opposite conclusion. There is little to say, beyond what we have already said, except that we respectfully disagree with his analysis of the FDCA, the FDA's regulations, and the specific context of this lawsuit. Numerous courts have concluded, over the course of decades, that the FDCA provides a floor, not a ceiling, for state regulation. See supra, 14-15. While the dissent cites favorably the minority view, we agree with the majority view. There is much to be said for the policy arguments employed by courts adopting this minority view, including the argument that permitting too much state activity in this area will make beneficial drugs less available to consumers. Similarly, there is merit to the majority perspective that eliminating lawsuits like the one at issue here would leave consumers without recourse in the event the FDA cannot move quickly enough to require strengthened warnings when they are appropriate. Our view is that neither policy argument is relevant here. The plain language of the statute indicates that Congress did not intend to interfere with state prerogatives except where doing so is absolutely necessary, see supra, 25-27, and the plain language of the regulation makes such interference unnecessary here, see supra, 12-13. This analysis is consistent with the constitutionally rooted presumption against preemption. To look more broadly at arguments relying on assumptions about safety and economic efficiency is to apply the opposite presumption-the presumption that Congress could not possibly have intended to allow states to intrude on what

seems, intuitively, to be an area of federal expertise. It is neither our responsibility, nor that of the FDA, to question the policy judgments of Congress. The litigation at issue here does not pose a direct and positive conflict with federal law, and thus, there is no basis for federal preemption.

2. The FDA's New Statement on Preemption

Defendant, after oral argument in this case, cited a new FDA regulation that contains a statement relating to the preemptive effect of the FDCA. The substance of the regulation changes certain aspects of labeling requirements for prescription drugs, but these changes are irrelevant to this appeal because the new rule did not take effect until June 2006. Food and Drug Administation, *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, Supplementary Information,* 71 Fed.Reg. 3922, 3922 (Jan. 24, 2006). The rule's "Supplementary Information" section, however, contains a broad statement regarding the preemption of state common-law failure-to-warn claims. *Id.* at 3933-36. In this statement, the FDA asserts that recent cases rejecting preemption of these claims, including those cited above, pose an obstacle to the agency's enforcement of the labeling requirements. Id. Among the interpretations the agency claims are incorrect are: (1) those rejecting preemption on the basis of ¶ 314.70(c); and (2) those stating that federal labeling requirements are minimum standards and that "[s]tate law serves as an appropriate source of supplementary safety regulation for drugs by encouraging or requiring manufacturers to disseminate risk information beyond that required by FDA under the act." *Id.* at 3934.

We are ordinarily required to defer to an agency's interpretation of a statute it administers. *Chevron, U.S.A., Inc. v. Natural Res. Def. Council*, 467 U.S. 837, 844, 104 S.Ct. 2778, 81 L.Ed.2d 694 (1984) ("We have long recognized that considerable weight should be accorded to an executive department's construction of a statutory scheme it is entrusted to administer...."). Plaintiff, however, urges us not to defer to the FDA's statement because it "was adopted without the requisite comment period" and "lack[s] the force of law." Presumably, if we were to credit plaintiff's argument, we would owe the statement only the limited deference due to agency statements made outside the agency's rulemaking authority. See *United States v. Mead Corp.*, 533 U.S. 218, 226-27, 121 S.Ct. 2164, 150 L.Ed.2d 292 (2001) (stating that Chevron deference applies only "when it appears that Congress delegated authority to the agency generally to make rules carrying the force of law, and that the agency interpretation claiming deference was promulgated in the exercise of that authority"). We need not decide this difficult question of administrative law, however, because we conclude that irrespective of the level of deference we might apply, the statement would not affect the outcome of this appeal.

Under Chevron, deference to an agency's interpretation is appropriate only when a statute is "silent or ambiguous with respect to the specific issue" the agency has considered; otherwise, "the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." 467 U.S. at 842-43. Moreover, "[t]he judiciary is the final authority on issues of statutory construction and must reject administrative constructions which are contrary to clear

congressional intent." *Id.* at 843 n. 9. "If a court, employing traditional tools of statutory construction, ascertains that Congress had an intention on the precise question at issue, that intention is the law and must be given effect." *Id.* When an agency's interpretation is not the type of interpretation entitled to Chevron deference, we must still grant it some respect, but only "a respect proportional to its 'power to persuade.'" *Mead*, 533 U.S. at 235 (quoting *Skidmore v. Swift & Co.*, 323 U.S. 134, 140, 65 S.Ct. 161, 89 L.Ed. 124 (1944)).

Under either standard, the FDA's statement deserves no deference. We have already concluded, supra 26-27, that Congress intended the FDCA to preempt only those state laws that would make it impossible for manufacturers to comply with both federal and state requirements. Nothing in the FDA's new statement alters our conclusion that it would be possible for defendant to comply with both its federal obligations and the obligations of state common law. The regulatory framework for prescription drug labeling allows drug manufacturers to add or strengthen a warning "to increase the safe use of the drug product" without prior FDA approval. See supra 10-13 (citing 21 C.F.R. ¶ 314.70(c)(6)(iii)(C)). Even if the new rule eliminated or altered this provision, the change in the regulation did not take effect until June 2006.[5] Without such a change, it is possible for manufacturers to comply with both FDA regulations and duties imposed by state common law, and there is no "direct and positive conflict" between state and federal law.

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5. The only alteration the new rule appears to make to ¶ 314.70 is that changes to the new "Highlights" section of a drug label may not be made without prior approval. 71 Fed.Reg. at 3934.

The FDA does not attempt to establish such a conflict or explain the inconsistency between its position and the language of the preemption amendment. The statement cites the amendment, but then proceeds as if Congress had not spoken on the issue of preemption. The agency relies on Geier to support its disregard of Congress's "direct and positive conflict" language, asserting that "[t]he existence of a legislative provision addressing pre-emption does not bar the operation ofordinary principles of implied preemption." 71 Fed.Reg. at 3935 (citing *Geier*, 529 U.S. at 869). Geier does state that implied preemption applies even when a statute addresses preemption expressly, 521 U.S. at 869, but it does not allow courts or agencies to preempt state laws that have been expressly preserved by Congress. Instead, it simply stands for the proposition that Congress's intent not to preempt a provision of state law cannot be inferred from either (1) an express preemption clause that does not include the state law in question in its scope, or (2) a clause that prevents regulated entities from using compliance with federal law as a defense in state common-law suits. *Id.* at 869-70. According to Geier, the former clause does not support a negative inference that Congress must have intended to preserve laws it did not expressly preempt; the latter indicates only that Congress intended to preserve some common-law claims, not that it intended to allow even claims that conflict with federal requirements. *Id.* But see id. at 870 (stating that even the latter clause would "preserve [ ] those actions that seek to establish greater safety than the minimum safety achieved by a federal regulation intended to provide a floor").

Here, we are not attempting to infer the effect of statutory language that only indirectly addresses the specific state law at issue. Instead, we are interpreting an unambiguous express preemption clause that specifically preserves the type of state law at issue. Under these circumstances, ordinary preemption principles must give way to Congress's intent to preserve state laws that do not create a "direct and positive conflict" with federal law. Drug Amendments ¶ 202. There is no such conflict here. Accordingly, the FDA's statement is neither an authoritative interpretation of an ambiguous statutory provision entitled to deference, *Chevron*, 467 U.S. at 842-43, nor a persuasive policy statement entitled to respect. *Mead*, 533 U.S. at 235. Plaintiff's claim does not impose conflicting obligations on defendant or present an obstacle to the objectives of Congress. We therefore agree with the trial court that the claim is not preempted by federal law.

II. Apportionment of Damages

Defendant next contends the court erred by failing to instruct the jury to reduce plaintiff's damages by the amount of fault attributable to the Health Center. "Reversing a jury verdict based on allegedly faulty jury instructions is warranted where the party claiming error establishes that the instructions were erroneous and prejudicial." *Simpson v. Rood*, 2005 VT 21, 5, 178 Vt. 474, 872 A.2d 306 (mem.). We hold that there was no error in the court's failure to require apportionment of damages between defendant and the Health Center.

Defendant argues that pursuant to Vermont's comparative negligence statute, a defendant is liable for only the portion of the plaintiff's damages attributable directly to that

defendant's negligence. 12 V.S.A. ¶ 1036. Our traditional rule is that multiple tortfeasors are jointly and severally liable. See *Zaleskie v. Joyce*, 133 Vt. 150, 158, 333 A.2d 110, 115 (1975) ("[T]he law of this state ... permits a plaintiff to pursue all, or any part, of his recovery from either joint tortfeasor"). According to defendant, ¶ 1036 applies not only under circumstances where comparative negligence is alleged on the part of the plaintiff, and not only when multiple defendants are sued in the same action, but also any time the plaintiff recovers from someone besides the defendant. Thus, because plaintiff and the Health Center reached a settlement in a separate lawsuit related to the same injury, defendant claims the jury should have been required to calculate the Health Center's proportion of causal negligence and subtract that percentage from the verdict.

Section 1036 states, under the heading of "Comparative negligence,"

> Contributory negligence shall not bar recovery in an action by any plaintiff, or his legal representative, to recover damages for negligence resulting in death, personal injury or property damage, if the negligence was not greater than the causal total negligence of the defendant or defendants, but the damage shall be diminished by general verdict in proportion to the amount of negligence attributed to the plaintiff. Where recovery is allowed against more than one defendant, each defendant shall be liable for that proportion of the total dollar amount awarded as damages in the ratio of the amount of his causal

> negligence to the amount of causal negligence attributed to all defendants against whom recovery is allowed.

12 V.S.A. ¶ 1036. We interpreted this statute under slightly different circumstances in *Plante v. Johnson*, 152 Vt. 270, 565 A.2d 1346 (1989). In Plante, the defendant resisted joinder of the plaintiffs' claims against her and a third party, resulting in a joint trial with two separate verdicts. The jury first returned a verdict against the third party for the entire amount of the plaintiff's damages, then found against the defendant for the same amount, and the court consolidated the judgments. The defendant appealed, arguing that the first verdict made the third party's share of the fault 100%. She concluded that under ¶ 1036, she was entitled to a ruling apportioning 100% of the liability for the plaintiff's damages to the third party. The defendant failed to argue this point at trial, making a holding regarding ¶ 1036 unnecessary. We nevertheless examined the statute in depth to demonstrate that our determination that the defendant was not entitled to apportionment was "more than a technical omission." *Id. at* 272, 565 A.2d at 1347. We concluded that the statute did not apply to the defendant in Plante because "the statute provides for apportionment among defendants, suggesting that only those joined in the same action should be considered in apportioning damages," and "there is no allegation that the plaintiff was negligent in this case."[6] *Id.* at 273, 565 A.2d at 1347-48.

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6. We also listed as an additional reason, not applicable here, that the third party whose liability was at issue in Plante was held liable under a different theory of liability that was not clearly within the scope of ¶ 1036. Id. at 273, 565 A.2d at 1348.

In reaching this conclusion, we relied in part on the fact that "the New Hampshire Supreme Court has held that its nearly identical statute does not apply to create several liability in the absence of an allegation of negligence on the part of the plaintiff." *Id.*, 565 A.2d at 1348 (citing *Lavoie v. Hollinracke*, 127 N.H. 764, 513 A.2d 316, 319-20 (N.H.1986)). Defendant points out that Lavoie has since been overruled, but the decision overruling it, *Nilsson v. Bierman*, 150 N.H. 393, 839 A.2d 25 (N.H.2003), relied on a legislative revision of New Hampshire's statute that placed the concepts of comparative negligence and apportionment under separate headings. *Id.* at 29. In the absence of action by the Legislature to amend Vermont's comparative negligence statute, we see no reason to depart from the interpretation of ¶ 1036 contained in Plante. The Health Center was not a party to plaintiff's action against defendant, and defendant does not allege that plaintiff was comparatively negligent, so ¶ 1036 does not apply in this case.

Defendant argues that whether or not ¶ 1036 applies, we can depart from our common law and determine that joint and several liability should no longer prevent apportionment among joint tortfeasors when one tortfeasor has settled in a previous action. We decline to do so. In *Howard v. Spafford*, 132 Vt. 434, 321 A.2d 74 (1974), which also involved an interpretation of ¶ 1036, we expressed our hesitation to depart from the rule precluding contribution among joint tortfeasors, preferring not to "substitute judicial fiat for legislative action." *Id.* at 435, 321 A.2d at 75. Among the many reasons cited in Howard for adhering to the common law was the sheer number of alternative schemes adopted by other states. *Id.* at 436-37, 321 A.2d at 75-76. This reasoning applies here

as well. Our choice is not between the traditional rule and a uniform new rule, but rather between a traditional rule and a number of potential new rules or combinations of rules. The Nilsson court pointed out the divide among states requiring jury verdicts to be reduced by the dollar amount of the plaintiff's settlement with a third party (pro tanto), those requiring verdicts to be reduced by the percentage of the settling party's fault (proportional share), and those requiring verdicts to be divided among all joint tortfeasors equally (pro rata). 839 A.2d 30-31. That court pointed out that while "[t]he American Law Institute favors the proportional share approach ..., the overwhelming majority of States reject the proportional share approach in favor of some version of the pro tanto approach," and New Hampshire's legislature chose a combination of the two. Id. at 31 (citations and quotations omitted). It is important to note that if we were to adopt the majority rule, our decision would have no effect on this case, as plaintiff and defendant have stipulated to a pro tanto reduction. Like the New Hampshire court, we will allow the Legislature to determine which approach is best, if it has not done so already by leaving ¶ 1036 in place after our interpretation in Plante.

III. Present Value of Damages

Finally, defendant contends the court erred by failing to instruct the jury to calculate the present vale of plaintiff's damages for future non-economic losses, such as pain and suffering. Defendant claims that the jury's verdict, which granted plaintiff $5 million in non-economic damages, exceeded the present value of plaintiff's requested amount by $856,073. In rejecting defendant's proposed instruction,

the court pointed out that defendant failed to provide the jury with expert guidance as to how present value should be calculated, and that "[j]udges and lawyers are universally incapable of performing the discount calculations with or without a calculator and the tables of historic interest rates and inflationary factors." We agree that it would have been inappropriate to instruct the jury to make such a calculation under these circumstances.

Even if defendant had presented testimony allowing the jury to make an informed calculation, we would have upheld the jury's verdict for several reasons. First, defendant's assertion that the jury did not take account of the present value of plaintiff's non-economic damages is pure speculation, as plaintiff's calculation of her economic damages was presented in terms of its present value, and "the jury was not required to demonstrate its calculations" with respect to plaintiff's non-economic damages. *Debus v. Grand Union Stores of Vt.*, 159 Vt. 537, 543, 621 A.2d 1288, 1292 (1993). Second, we limit pre-judgment interest to economic damages because non-economic damages are "inchoate and rarely ascertainable at the time of injury." *Turcotte v. Estate of LaRose*, 153 Vt. 196, 200 n. 2, 569 A.2d 1086, 1088 n. 2 (1989). These damages become no less inchoate following a judgment, and we will not require juries to apply a precise economic calculation to a figure we have identified as inherently imprecise.

Finally, most jurisdictions and the Restatement (Second) of Torts reject the concept of requiring juries to make present-value calculations with respect to non-economic damages. See, e.g., *Taylor v. Denver & Rio Grande W. R.R.*, 438 F.2d

351, 353 (10th Cir.1971) (holding that instruction requiring present-value reduction for pain and suffering was error and stating that most courts that have considered the issue have decided "that the better reasoned authority supports the rule that future pain and suffering should not be reduced to current worth"); Restatement (Second) of Torts ¶ 913A cmt. a (1979) (stating that while future pecuniary losses should be reduced to present value, "an award for future pain and suffering or for emotional distress is not discounted in this fashion"). But see *Olivieri v. Delta S.S. Lines, Inc.*, 849 F.2d 742, 750-51 (2d Cir.1988) (stating that "[i]f we were writing on a clean slate, we might be inclined to accept the view of the other circuits and reject any discounting of future non pecuniary losses," but previous Second Circuit holdings required such discounting in some form). Defendant's reliance on our decision in *Parker v. Roberts*, 99 Vt. 219, 131 A.2d 21 (1925), is misplaced, as Parker, while it required a jury instruction on the present value of future losses, did not address the distinction between pecuniary and non-pecuniary losses. *Id.* at 224-25, 131 A. 21, 131 A.2d at 23. The trial court did not err in refusing to instruct the jury to reduce plaintiff's non-economic damages to present value.

Affirmed.

Associate Justice

Appendix A

Dissenting

REIBER, C.J., dissenting. The overarching issue in this appeal is whether plaintiff's common-law claim for failure to warn conflicts with the FDA's regulation of Phenergan, the drug responsible for plaintiff's injuries. I would conclude that the jury's verdict in this case conflicts with federal law for two reasons.

First, it would be impossible for defendant Wyeth to comply with the requirements of both state and federal law. Specifically, the FDA approved IV administration of Phenergan and required that IV administration be listed on the Phenergan label. By contrast, plaintiff's theory of the case required Wyeth either to remove this approved use from the Phenergan label, add a warning that would directly contradict the label's indication that IV administration was a safe and effective use, or, at a minimum, add a warning that only certain types of IV administration should be used. Thus, compliance with state law in this case would require Wyeth to eliminate uses of Phenergan approved by the FDA and required to be included in the Phenergan labeling.

Second, plaintiff's state-law claim conflicts with federal law in that it poses an obstacle to federal purposes and objectives. In short, by approving Phenergan for marketing and distribution, the FDA concluded that the drug-with its approved methods of administration and as labeled-was both safe and effective. See 21 U.S.C. ¶ 355(d) (listing criteria for drug approval). In finding defendant liable for failure to warn, a Vermont jury concluded that the same drug-with its approved methods of administration and as labeled-was "unreasonably dangerous." See *Town of Bridport v. Sterling*

Clark Lurton Corp., 166 Vt. 304, 308, 693 A.2d 701, 704 (1997) (to succeed on failure-to-warn claim, plaintiff must show that "failure to warn made the product unreasonably dangerous and therefore defective"). These two conclusions are in direct conflict.

For both of these reasons I would conclude that the state-law cause of action is preempted. I respectfully dissent.

I. Impossibility of Compliance

As explained by the majority, because there is no clause in the FDCA expressly preempting state law, Wyeth must demonstrate that preemption is implied by showing either that federal law thoroughly occupies the regulatory field (a claim that Wyeth does not advance) or that there is an actual conflict between state and federal law. Actual conflict, in turn, can be demonstrated in one of two ways: by showing that it is impossible for the regulated party to comply with both state and federal law or that state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Freightliner Corp. v. Myrick*, 514 U.S. 280, 287, 115 S.Ct. 1483, 131 L.Ed.2d 385 (1995) (quotations omitted).

The majority in essence concludes that it is not impossible for Wyeth to comply with both federal and state standards because Wyeth never sought FDA approval of a "stronger warning" of the type advocated by plaintiff. According to the majority, because the FDA was not presented with, and therefore did not explicitly reject, such strengthened language, there is no reason to presume that

the FDA would disapprove. Therefore, the majority reasons, there is no actual conflict between state and federal law. See ante ¶ 21-22. It is inaccurate, however, to characterize the requirements imposed by the jury verdict in this case as merely requiring a "stronger warning." Rather, what plaintiff sought was an elimination of a use of Phenergan that had been approved by the FDA. Furthermore, the FDA's rejection of Wyeth's efforts to alter the language of the warning in 2000 supports Wyeth's claim that the FDA had an affirmative preference for the language of the original warning.

A.

The crux of plaintiff's claim was not based on the label warnings per se, but on the approved uses listed there. See, e.g., ante ¶ 3 ("Plaintiff's experts testified that the label should not have allowed IV push as a means of administration...."). A review of plaintiff's complaint and the evidence presented at trial makes clear that the standard plaintiff sought to establish (i.e., the change to the label that would be required in light of the jury's finding of liability) was to remove IV administration-or at least certain types-as an approved use. For example, plaintiff's complaint asserted that the warnings on the label were inadequate and that:

> [t]he Phenergan sold by defendant is ... NOT REASONABLY SAFE FOR INTRAVENOUS ADMINISTRATION because the foreseeable risks of harm posed by intravenous administration of the drug are sufficiently great in relation to its foreseeable theraputic benefits that reasonable health care providers, knowing of such foreseeable

> risks and benefits, WOULD NOT PRESCRIBE THE DRUG INTRAVENOUSLY FOR ANY CLASS OF PATIENTS."

(Emphasis added.) In her appellate brief, plaintiff characterizes the evidence as revealing "that Wyeth was aware of research indicating that DIRECT IV ADMINISTRATION OF PHENERGAN WAS UNSAFE." (Emphasis added.) Plaintiff further refers to expert testimony "that the LABEL SHOULD HAVE RESTRICTED PHENERGAN TO INTRAMUSCULAR INJECTION as this method of administration presents no risk of inadvertent arterial injection; or, alternatively, that if IV administration is used, it must be by injecting the Phenergan into a hanging IV bag, not through a direct IV." (Emphasis added.)

Here, the FDA clearly addressed the risks attending IV administration of the drug. The label approved IV administration generally, and specifically warned of the dangers of direct IV administration, including inadvertent arterial injection possibly resulting in amputation. In light of this, it cannot be argued that the FDA did not (1) assess the risk of IV administration, including direct IV administrationand the associated risk of amputation due to inadvertent arterial injection; (2) conclude that the benefits of allowing IV administration with appropriate warnings outweighed the risk; and (3) reach a decision regarding precisely what warning language should be used. These assessments are, in fact, the very essence of the FDA's approval and are in furtherance of the federal objective of advancing public health by balancing the risks and benefits of new drugs and facilitating their optimal use. See 21 U.S.C.

¶ 355(d) (listing factors to be considered in approving or refusing new drug application); 21 U.S.C. ¶ 393(b)(1), (b)(2)(B) (FDA is charged with promoting public health by acting promptly on new drug applications and protecting public health by ensuring that new drugs are both safe and effective).

The majority reconciles this manifest conflict by relying on 21 C.F.R. ¶ 314.70(c), which allows a drug manufacturer to alter a label "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction" or "add or strengthen an instruction about dosage and administration" prior to FDA approval.[7] On this basis, the majority concludes that Wyeth "was free under ¶ 314.70(c) to strengthen the warning without prior FDA approval." Ante ¶ 22. But, it is an overstatement to claim that manufacturers are "free" to change drug labels under ¶ 314.70(c). To the contrary, a manufacturer may change a label only to add or strengthen a warning, not to eliminate an approved use, as plaintiff would require here. In other words, what plaintiff advocates is not a stronger warning but language that would directly contradict language approved and mandated by the FDA.

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7. This is also the approach employed by the numerous federal district court decisions cited by the majority. Ante ¶ 14, 565 A.2d 1346. Because I disagree with this analysis of the import of ¶ 314.70(c), I do not find these decisions to be persuasive. Instead, I side with the minority view expressed in Needleman, which concludes that ¶ 314.70(c) gives manufacturers very little latitude in unilaterally revising drug labels. *Needleman v. Pfizer, Inc.*, 2004 WL 1773697, at *3 (N.D.Tex.).

Further, the apparent purpose of ¶ 314.70(c) is to allow manufacturers to address newly-discovered risks. See 44 Fed.Reg. 37434, 37447 (June 26, 1979) (allowing supplement to label "whenever possibly harmful adverse effects associated with the use of the drug are discovered"). Even courts that conclude that ¶ 314.70(c) provides manufacturers broad latitude to add warnings to labels acknowledge that such supplements are aimed at previously unknown and unanalyzed risks. See *McNellis v. Pfizer, Inc.*, 2005 WL 3752269, at *6 (D.N.J.) (concluding that ¶ 314.70(c) "was promulgated precisely to allow drug manufacturers to quickly strengthen label warnings when evidence of new side effects [is] discovered") (citing 30 Fed.Reg. 993 (Jan. 20, 1965)); *Kurer v. Parke, Davis & Co.*, 2004 WI App 74, 18, 272 Wis.2d 390, 679 N.W.2d 867 (noting that, under ¶ 314.70(c), "[d]rug manufacturers can strengthen warnings or petition for additional warnings when new risk information arises"). Another section of the regulation makes clear that any changes to a label that exceed the scope of ¶ 314.70(c) are considered "major changes" that require prior approval before the drug may be distributed. ¶ 314.70(b), (b)(2)(v). In short, the regulation does not allow manufacturers to simply reassess and draw different conclusions regarding the same risks and benefits already balanced by the FDA. Here, the FDA had already evaluated the risk of inadvertent arterial injection from direct IV administration of Phenergan, and had mandated warning language for the label to reflect that risk assessment.

In addition, any change accomplished under ¶ 314.70(c) is subject to ultimate FDA review and approval. See ¶ 314.70(c)(7) (providing that FDA may order manufacturer

to cease distribution of drug if it disapproves supplemental application); see also *Needleman v. Pfizer, Inc.*, 2004 WL 1773697, at *3 (N.D.Tex.2004) (noting that changes to label under ¶ 314.70(c) are temporary and "must later be approved by the FDA"). Thus, any additional or different warnings must ultimately be supported by scientific research that meets the FDA's standards. Neither a manufacturer, a state court, nor a state legislature can permanently substitute its judgment of the risk-benefit analysis for that of the FDA.

At its core, plaintiff's argument in this case was not that the warnings on the label were inadequate, but that an approved use (direct IV administration) was in fact unreasonably unsafe. Plaintiff did not seek to "add or strengthen" a warning or a dosage/administration instruction, but rather to eliminate an approved use of the drug. This is a disagreement that cannot be overcome by operation of ¶ 314.70(c). Plaintiff's claim in this case-that a method of administration of the drug should be partially if not entirely eliminated from the labeling-represents a substantive disagreement with FDA policy that goes beyond labeling/warning issues alone. This disagreement creates opposing requirements and a manufacturer could not satisfy both at once.

B.

Wyeth argues that even if ¶ 314.70(c) theoretically allows a manufacturer to make unilateral changes to a drug label, in this case, the FDA actually rejected Wyeth's attempts in 2000 to change the warning regarding intra-arterial injection and amputation. The trial court concluded that the FDA gave only

"passing attention" to the risks of IV administration in 2000. Ante ¶ 4. The majority similarly concludes that the record does not indicate "that the FDA wished to preserve the use of IV push as a method of administering Phenergan." Ante ¶ 23. I cannot agree with this assessment of the record.

Both the original label and Wyeth's proposed alternative were titled "INADVERTENT INTRA-ARTERIAL INJECTION." On the original label, the first two sentences of the warning read:

> Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injection of [Phenergan], usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances.

On the proposed label, the first sentence of the warning read: "There are reports of necrosis leading to gangrene, requiring amputation, following injection of [Phenergan], usually in conjunction with other drugs; the intravenous route was intended in these cases, but arterial or partial arterial placement of the needle is now suspect." While the proposed change to the warning language may not reflect what plaintiff would require in a warning, it cannot be disputed that Wyeth's proposed alternative warning (1) placed greater emphasis on

the risk of necrosis and amputation by referencing it in the first sentence, and (2) gave the FDA the opportunity to consider the specific, alternative warning advanced by Wyeth, as well as the adequacy of the warning in general. Despite this opportunity, the FDA mandated that Wyeth retain the language of the existing warning. The alleged extent of the FDA's consideration of the issue is not relevant, in my view.

In 2000, the FDA confirmed its assessment that health care professionals should be permitted to choose IV administration in its various forms as a means of delivering the drug, where appropriate. Wyeth could not both list all forms of IV administration as an approved use, as required by the FDA, and exclude all or some forms of IV administration as unsafe, as required by the jury's verdict in this case. It would be impossible to comply with both requirements.

II. Obstacle to Federal Purposes and Objectives

I would further conclude that Wyeth has demonstrated actual conflict preemption by showing that plaintiff's state-law failure-to-warn claim poses an obstacle to federal purposes and objectives. The majority does not address this issue, concluding that Wyeth does not have the option of proving this form of actual conflict preemption. The majority reaches this conclusion by relying on the following clause in the 1962 amendments to the FDCA:

> Nothing in the Amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law ... unless there is a direct and positive conflict between such amendments and such provision of state law.

Ante ¶ 26 (quoting Drug Amendments of 1962 (Harris Kefauver Act), Pub.L. No. 87 781, ¶ 202, 76 Stat. 780, 793 (1962)). Citing *Southern Blasting Services, Inc. v. Wilkes County*, 288 F.3d 584, 591 (4th Cir.2002), the majority concludes that the provision "essentially removes from our consideration the question of whether common-law tort claims present an obstacle to the purposes and objectives of Congress," because the 1962 provision "simply restates the principle that state law is superseded in cases of actual conflict with federal law such that compliance with both federal and state regulations is a physical impossibility." Ante ¶ 27 (internal quotations omitted). "In other words," the majority explains, "under any circumstances where it is possible to comply with both state law and the FDCA, the state law in question is consistent with the purposes and objectives of Congress." Id. Thus, the majority eliminates the possibility of proving actual conflict preemption independently through the "obstacle" prong of that standard.

But neither the passage in Southern Blasting on whichthe majority relies nor the United States Supreme Court decision[8] cited as authority in that passage provide an explanation or

8. See *Hillsborough v. Automated Med. Labs.*, 471 U.S. 707, 713, 105 S.Ct. 2371, 85 L.Ed.2d 714 (1985). The cited passage in Hillsborough does not interpret the phrase "direct and positive conflict." It merely cites the different forms of preemption, including the "obstacle" prong. It is worth noting that the federal statute at issue in *Geier v. American Honda Motor Co.*, 529 U.S. 861, 120 S.Ct. 1913, 146 L.Ed.2d 914 (2000) (discussed below), contained an even broader savings clause than the 1962 amendment to the FDCA. The provision in Geier stated simply that the federal safety standard at issue did "not exempt any person from any liability under common law." *Id.* at 868.

even an affirmative statement that the phrase "direct and positive conflict" in the 1962 amendment eliminates the "obstacle" prong of the actual conflict preemption standard. Thus, the majority eliminates one of the two means by which Wyeth may show actual conflict based on a single, unclearly-reasoned Fourth Circuit decision that is itself lacking in case law support. There is no basis for eliminating this prong of the actual conflict standard, and I disagree with the majority's conclusion to the contrary.[9]

Assuming, then, that Wyeth may demonstrate actual conflict preemption by showing that state law is an obstacle to federal regulatory purposes and objectives, I believe the facts here support the conclusion that the state tort-law verdict in this case is preempted. The United States Supreme Court's decision in *Geier v. American Honda Motor Co.*, 529 U.S. 861, 120 S.Ct. 1913, 146 L.Ed.2d 914 (2000), is controlling on the question of when state law poses an obstacle to federal purposes and objectives. In that case, the Department of Transportation had issued a safety standard that required automobile manufacturers "to equip some but not all of their 1987 vehicles with passive restraints." *Id.* at 864-65. Among the optional passive restraints were air bags. Honda was in

9. Nonetheless, the Court concluded that all ordinary preemption principles-including actual conflict preemption and the obstacle prong of the standard-applied. The Court rejected the notion that Congress would so limit the effect of preemption as to allow an actual conflict with a federal objective: "Insofar as petitioners' argument would permit common-law actions that 'actually conflict' with federal regulations, it would take from those who would enforce a federal law the very ability to achieve the law's congressioally mandated objectives that the Constitution, through the operation of ordinary pre-emption principles, seeks to protect." *Id.* at 872.

compliance with this standard. Nonetheless, the plaintiff was seriously injured in a car accident while driving a 1987 Honda that was not equipped with an air bag, but with another form of passive restraint. The plaintiff brought suit, alleging Honda was negligent in failing to install a driver's-side air bag in the car. Honda argued that the federal safety standard preempted the plaintiff's state-law negligence claim. The Supreme Court held that a lawsuit premising negligence on the failure to install an air bag conflicted with the objectives of the federal safety standard and was therefore preempted. *Id.* at 866.

In reaching this conclusion, the Court noted that the plaintiff and the dissenting opinion-like the majority in the instant case-viewed the federal regulation as setting a minimum safety standard that states were free to supplement or strengthen. *Id.* at 874. However, by examining the comments accompanying the regulation, the Court concluded that a safety standard allowing a choice of passive restraint systems while not mandating any particular system was a deliberate decision that reflected a balance of diverse policy concerns. See *id.* at 875 (noting that allowing mix of available safety devices available over time would "lower costs, overcome technical safety problems, encourage technological development, and win widespread consumer acceptance"). "In sum, ... the 1984 version of [the safety standard] embodies the Secretary's judgment that safety would best be promoted if manufacturers installed alternative protection systems in their fleets rather than one particular system in every car." *Id.* at 881 (quotations omitted). Accordingly, the Court concluded that the tort action sought to impose a duty on manufacturers to impose air bags, rather than other types of

passive restraint systems, and that this state-law requirement was an obstacle to the federal objective of allowing a mix of safety devices.

Application of the Supreme Court precedent in Geier dictates the same result in this case. As with the DOT in Geier, the FDA is primarily concerned with public safety. The conclusion of what is best for public safety is arrived at by considering various policy factors that are sometimes in tension with one another. For example, in developing the safety regulation at issue in Geier, the DOT considered not only which passive-restraint systems were safest on an absolute scale, but which were most cost-effective and which would gain consumer acceptance. Similarly, here the FDA balances its assessment of a drug's safety against concerns for the drug's efficacy, taking into account that a safer but less effective drug is not necessarily best for the public health overall. See 21 U.S.C. ¶ 355(d) (FDA must consider safety and efficacy); 21 U.S.C. ¶ 393(b)(1), (b)(2)(B) (FDA's mission is to protect public from unsafe drugs and to promote public health by approving regulated products in timely manner). In the specific context oarnings on drug labels, the FDA considers not only what information to include, but also what to exclude. As the Eighth Circuit has noted in the medical device context, "[t]here are ... a number of sound reasons why the FDA may prefer to limit warnings on product labels." See *Brooks v. Howmedica, Inc.*, 273 F.3d 785, 796 (8th Cir.2001). For example, "warning about dangers with less basis in science or fewer hazards could take attention away from those that present confirmed, higher risks." *Id.*

Appendix A

No drug is without risks. The FDA balances the risks of a drug against its benefits to maximize the availability of beneficial treatments. The FDA's decision in approving a drug, its uses and labeling reflect consideration of these and other policy factors. While a state-court jury presumably shares the FDA's concern that drugs on the market be reasonably safe, the jury does not assess reasonableness in the context of public health and the associated risk-benefit analysis. A jury does not engage in a measured and multi-faceted policy analysis. Rather, a jury views the safety of the drug through the lens of a single patient who has already been catastrophically injured. Such an approach is virtually guaranteed to provide different conclusions in different courts about what is "reasonably safe" than the balancing approach taken by the FDA. In act, different conclusions were reached in this case.

The jury in this case was instructed that "[a] prescription drug is unreasonably dangerous due to inadequate warnings or instructions if reasonable instructions regarding foreseeable risks of harm are not provided to the physician and other medical professionals who are in a position to reduce the risks of harm." Faced with plaintiff's tragic injuries, the jury concluded that allowing *Phenergan* to be delivered through IV administration was "unreasonably dangerous." The jury's verdict conflicts squarely with the FDA's assessment of precisely the same issue: whether *Phenergan* is safe and effective when delivered through IV administration. The claim is preempted.

For the above reasons, I dissent.

Chief Justice

APPENDIX B — DECISION OF THE SUPERIOR COURT OF WASHINGTON COUNTY FILED AUGUST 2, 2004

STATE OF VERMONT
COUNTY OF WASHINGTON, SS.

Washington Superior Court
Docket No.: 670-12-01

DIANE LEVINE,

Plaintiff,

v.

AMERICAN HOME PRODUCTS, INC.
(now WYETH),

Defendant.

DECISION ON MOTION FOR JUDGMENT UNDER V.R.C.P. 50

This is a motion for judgment under Rule 50 following entry of judgment in a product liability case. The motion was timely filed and follows an earlier motion for judgment on the same grounds submitted at the close of the evidence.

Factual Background

This case arises out of an incident on April 7, 2000, when plaintiff received an injection of the drug Phenergan from physician's assistant Jessica Fisch at the Health Center in Plainfield, Vermont. Phenergan is an anti-nausea medication

manufactured and sold by defendant. As a result of the injection, plaintiff developed gangrene in her right hand. She underwent an amputation of her right arm at the elbow. Plaintiff settled a separate claim against the Health Center and her physician prior to suit.

The parties tried this case from March 8–March 11, 2004. The jury verdict was for $7,400,000. The parties stipulated to adjustments for the prior settlement and pre-judgment interest. The Court entered judgment on March 17, 2004, for $6,774,000.

Standard of Review

The standard of review for a Rule 50 motion is whether "during a trial by jury a party has been fully heard on an issue and there is no legally sufficient evidentiary basis for a reasonable jury to find for that party on that issue." V.R.C.P. 50(a). If the basis for the jury's verdict is insufficient, "the court may determine the issue against that party." *Id.* The trial court may grant the motion against a party "with respect to a claim or defense that cannot under the controlling law be maintained or defeated without a favorable finding on that issue." *Id.*; see also *Brueckner v. Norwich University*, 169 Vt. 118, 122 (1999) ("[A] trial court considers the evidence in the light most favorable to the nonmoving party, excluding the effect of any modifying evidence.") (citation omitted).)

Appendix B

I. Federal Preemption by FDA approval of Phenergan labeling

Plaintiff's claim against defendant is based on allegations that defendant failed to warn of the hazards of intravenous injection of Phenergan. At trial plaintiff introduced evidence that Phenergan should be administered by intra-muscular injection or through a free-flowing IV bag. Plaintiff's witnesses testified that injection into the patient's vein through a "butterfly" infusion set was too dangerous and should have been strongly discouraged in the instructions for use – the "package insert" or label which accompanies the product when it is provided to a physician.

Defendant argues that the approval of the Phenergan label by the Food and Drug Administration preempts Vermont product liability law on the issue of labeling and provides a defense as a matter of law to a claim based on failure-to-warn.

Factual Record at Trial

At trial defendant received wide latitude to introduce evidence about its interaction with the FDA concerning the Phenergan label. The factual record relevant to the Rule 50 motion is as follows:

1. The corrosive nature of Phenergan can lead to catastrophic tissue damage if it enters a patient's arterial blood flow. As the arteries become smaller and more diffuse, the tiny vessels can be damaged by exposure to Phenergan. The patient suffers spasm of the arteries, inflammation, loss of blood flow due

to clotting, gangrene, and, in some cases, the loss of a limb or other serious injury. Green. Tr. 212, 216. Once Phenergan enters the arterial flow, there is no reliable way to reverse the harmful effects of the medication on the tiny vessels distal (downstream) from the site of the injection. Green Tr. 213.

2. In this case, plaintiff received an injection of Phenergan through the use of a "butterfly" intravenous infusion set. The butterfly set consists of a needle which is placed in the patient's vein and held in place by two flexible tabs – the "butterfly." The infusion set creates a fixed point of entry into the vein. Medication can then be injected through the infusion set into the patient's vein. Alternatively, the infusion set can be hooked up to a free-flowing IV bag. Medication such as Phenergan can be added to the IV solution and administered through the IV drip. Matthews, Tr. 85–100. Ms. Fisch injected 50 milligrams of Phenergan directly through the butterfly infusion set into plaintiff's arm over the course of several minutes. She did not use a free-flowing IV bag. Matthews, Tr. 89–93.

3. For reasons that remain unclear, the Phenergan entered plaintiff's arterial system, either because the needle in the infusion set entered an artery directly or because the drug leaked out of the vein and entered an artery through a process called extravasation. Green Tr. 211. As a result of the injection, plaintiff suffered catastrophic injury to her right arm.

4. One way to reduce the risk of inadvertent intra-arterial injection is to set up a free-flowing IV bag and introduce the drug into the IV solution. This is an alternative to injection

through the infusion set into a patient's vein. Administration through a free-flowing IV bag reduces the risk of inadvertent arterial injection because the nurse or physician can be more certain that the needle has been placed in a vein. A solution dripping from an IV bag will not flow freely into an artery due to back pressure from the patient. Green Tr. 194–98, 208–14.

5. The FDA has approved the label for Phenergan since at least 1974. Defendant Ex. P.

6. Since at least 1976, both the FDA and defendant have recognized that injection of Phenergan into an artery is dangerous and can result in severe injury. Defendant Ex. R. By 1976, the Phenergan label contained specific warnings about the hazard of intra-arterial injection. Defendant Ex. S.

7. The minutes of an FDA anesthesiology advisory committee meeting on 10/14/76 include discussion of the Phenergan label then in use. The committee considered a variety of concerns including the risk of intra-arterial injection. The committee recommended that an additional warning should be added: "If a Tubex system is used for intravenous injection, the drug should be injected into a satisfactorily functioning intravenous set." Ex. S.

8. In 1979, the FDA required extensive relabeling of pharmaceutical drugs, including Phenergan. The defendant gave some consideration to changing the warnings about intra-arterial injection to recommend use of an intravenous infusion set for administration of the drug. A 1981 proposed package insert contained the following language:

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> When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

Ex. T. Defendant submitted the same proposed language to the FDA on 5/3/88 in conjunction with other proposed changes to the Phenergan label. Ex. M. The proposed language was never used.

9. In a letter to defendant dated 2/21/97, an FDA official directed defendant to "retain verbiage in current label" with respect to the risk of inadvertent intra-arterial injection. No warning or instruction concerning the preferred use of an intravenous infusion set appeared in the defendant's label, including the label in use when the dose of Phenergan involved in this case was sold.

10. The letter dated 2/21/97 identifies the "current label" as the version which defendant submitted to the FDA by letter on 8/6/96. The defendant was unable to obtain a copy of the 8/6/96 letter until after the completion of the trial. The Court will accept and consider this post-trial filing as it relates to the issue of preemption. Preemption is an issue for the Court, not the jury. The post-trial filing removes an area of confusion identified by the Court in the summary judgment decision dated 12/23/03.

11. The 8/6/96 letter from defendant to the FDA contains minor revisions of an earlier label submitted in 1992. It confirms that in 1997, the FDA approved various label changes for Phenergan and rejected the language which

defendant proposed in 1981 and 1988 concerning the preferred use of an intravenous infusion set for administering irritant drugs.

12. Plaintiff's expert witness Harold Green, M.D. testified that the warnings and instructions on the Phenergan label at the time of plaintiff's injury were inadequate to make the product safe because the defendant did not warn sufficiently of the risk of intravenous injection. Dr. Green testified that there was little medical justification for administration of Phenergan intravenously because of the availability of an intramuscular injection. If a physician chose intravenous administration of the drug, the use of a free-flowing IV bag would be safer than injection through a butterfly infusion set. Green Tr. 232–33.

13. Defendant's expert witness David Greenblatt, M.D. disagreed with Dr. Green. He testified that the clinician should remain free to decide whether to administer Phenergan intravenously instead of by intramuscular injection. Greenblatt Tr. 26–27. Dr. Greenblatt agreed with Dr. Green that it was safer to administer Phenergan through a free-flowing IV than by direct intravenous injection. Greenblatt, Tr. 49. Dr. Greenblatt testified that the butterfly infusion set could be considered to be a form of free-flowing IV administration. Greenblatt, Tr. 49.

Analysis

In any preemption case, the only issue is whether Congress intended to exercise the authority provided by the Supremacy Clause to serve as the exclusive source of law. U.S. Const.

art. VI, cl. 2; see also M. Carrier, *Federal Preemption of Common Law Tort Awards by the Federal Food, Drug, and Cosmetic Act*, 51 Food & Drug L.J. 509, 510–11 (1996). In a system in which federal and state law frequently overlap and occupy the same ground, the Supreme Court has consistently required restraint from the lower courts in striking down state remedies. See, e.g., *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 249–57 (1984) (allowing state court imposed punitive damages against nuclear rod manufacturer despite extensive federal regulation over atomic energy). The issue is defined by and limited to the search for Congressional intent expressed in specific legislation. Preemption analysis does not depend upon whether a judge believes that federal regulation of conduct is preferable for reasons of consistency or greater technical expertise.

The starting point for any analysis is the basic assumption that Congress did not intend to displace state law in passing legislation. *Maryland v. Louisiana*, 451 U.S. 725, 746 (1981). "Thus, while state action is preempted if it specifically frustrates the objectives, narrowly and concretely defined, that underlie federal enactments, no such conclusion follows where the most that can be said is that the direction in which state law pushes someone's actions is in general tension with broad or abstract goals that may be attributed to various federal laws or programs." L. Tribe. American Constitutional Law 1187 (3d ed. 2000). The Supreme Court has stated that there is a strong presumption that "the historic police powers of the States [are] not to be superseded by Federal Act unless that [is] the clear and manifest purpose of Congress." *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218 (1947); but cf. *Hines v. Davidowitz*, 312 U.S. 52 (1941) (finding federal supremacy

in the field of foreign affairs preempted a Pennsylvania statute requiring foreign aliens to register). In areas of health and safety, the U.S. Supreme Court has long recognized the primary interest of the states in the protection of their citizens. *Florida Lime & Avocado Growers v. Paul*, 373 U.S. 132, 144 (1963).

Congress has enacted preemption legislation in other related fields such as medical devices, 21 U.S.C. § 360k, and cigarette labeling, 15 U.S.C. § 1334, but it has not passed any legislation creating an area of *express* preemption for pharmaceutical labeling. See *Hurley v. Lederle Labs.*, 863 F.2d 1173, 1176 (5th Cir. 1988) (collecting decisions finding no express preemption for pharmaceutical labeling). When Congress has not enacted an express preemption provision, the courts must consider whether its intent to preempt state law can be fairly *implied*. The traditional bases for *implied* preemption are: (1) a comprehensive regulatory scheme which occupies the field so completely as to leave no room for state action (field preemption); (2) state law which obstructs the purpose of federal legislation (obstruction conflict preemption); or (3) a direct conflict between state and federal law (direct conflict preemption). *Hillsborough County, Fla. v. Automated Medical Laboratories*, 471 U.S. 707, 713 (1985). Under this standard, defendants argue that the breadth of FDA activity and the potential for interference with its regulatory decisions creates a basis for *implied* presumption. The breadth of activity is a basis for a claim of *field* preemption. The potential for interference is a basis for claims of *conflict* preemption. The Court will address each separately.

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Field Preemption

Since 1906, the Food and Drug Administration – then functioning as the Bureau of Chemistry – has reviewed and approved pharmaceutical labels under Congressional authority. 1906 Food and Drugs Act, ch. 3915, 34 Stat. 768 (repealed by the Federal Food, Drug, and Cosmetic Act of 1938, codified at 21 U.S.C. §§ 301 *et seq.* (2000)). The regulation of labeling is mandatory. Even minor changes require FDA approval. At the same time that the FDA has regulated pharmaceutical labels, plaintiffs in every state have filed tort claims against drug manufacturers on common law causes of action – principally strict liability for failure-to-warn. See, e.g., *McCallister v. Purdue Pharma L.P.*, 164 F.Supp. 2d 783, 787 (S.D. W. Va. 2001).

FDA regulation and state law tort remedies have co-existed for decades – generally to the consternation of the manufacturers. Despite countless "failure-to-warn" cases, filed over several decades, defendants have not identified an authoritative line of cases in which FDA regulation of pharmaceutical labels has been held to preempt the state law remedy of strict liability.

The evidence in this case demonstrates that FDA regulation of labeling is mandatory and comprehensive. It has long operated in conjunction with state law tort claims. Both the Restatement (Second) and Restatement (Third) of Torts: Product Liability permit manufacturers to offer evidence of compliance with FDA requirements as evidence of lack of defect. Restatement (Third) of Torts: Product Liability § 4 (1998); Restatement, Second, of Torts § 288c (1965).

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Compliance with the FDA regulations alone has never been held to be a bar as a matter of law to state law claims that a manufacturer failed to provide an adequate warning. Compare *Caraker v. Sandoz Pharmaceuticals Corp.* 172 F. Supp. 2d 1018, 1030–39 (S.D. Ill. 2001), with *McCallister*, 164 F. Supp. 2d at 792–93 (noting some preemption implications of the Controlled Substances Act).

The absence of an express preemption provision in the enabling legislation for FDA regulation is strong evidence that Congress has chosen not to preempt state law remedies in the area of pharmaceutical labeling. Cf. *Jones v. Rath Packing Co.*, 430 U.S. 519, 537 (1977) ("If Congress had intended to overrule this longstanding . . . practice, founded on a legislative statement of necessity, we would expect it to have done so clearly."); but cf. *Hurley*, 863 F.2d at 1179 (suggesting that the pervasiveness of FDA label regulations would preempt state action involving the adequacy of vaccines warnings). The *express* preemption provisions for medical devices, 21 U.S.C. § 360k, cigarettes 15 U.S.C. § 1334, and pesticides 7 U.S.C. § 136v(b), (FIFRA), demonstrate that Congress knows how to enact preemptive legislation when necessary. Se *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 518–20 (1992) (interpreting express statutory preemption). These are obviously different than the implied preemption cases because Congress has spoken aloud and expressly on the issue.

The great majority of courts considering the issue have held that state law claims are not preempted by the dominant presence of the FDA in the field. See *Caraker*, 172 F.Supp. 2d at 1038–39; *Foyle v. Lederle Labs.*, 674 F.Supp 530, 533

(E.D.N.C. 1987); *Carlin v. Superior Court*, 920 P.2d 1347, 1352–53 (Cal. 1996); *Washington State Physicians Ins. Exch. & Assoc. v. Fisons Corp.*, 858 P.2d 1054, 1069 (Wash. 1993); *Feldman v. Lederle Labs*, 625 A.3d 1066, 1070 (N.J. 1993); *Plenger v. Alza Corp.*, 13 Cal.Rptr. 2d 811, 819 n.7 (1992); but see *Ehlis v. Shire Richwood, Inc.*, 233 F. Supp.2d 1189, 1197–98 (D.N.D. 2002) (dicta suggesting preemption through the medical device amendment might apply). The sheer number of these decisions demonstrates that this is not a new issue on which Congress has not had an opportunity to act.

The requirement that pharmaceutical labels be approved by the FDA is insufficient to overcome the presumption against implied preemption. This Court finds no basis for denying plaintiff her remedies under state law on the basis of field preemption.

Conflict Preemption – Obstruction

Whether state law damage claims actually impede the FDA in the pursuit of its mission is hard to see from the limited context of a single personal injury trial. Successive political administrations have differed on this issue. In 1998, the FDA posted its final version of new rules governing the labeling of prescription drugs and clarified that the rules did not in any way preempt tort liability or a manufacturer's duty to warn. *Prescription Drug Product Labeling; Medication Guide Requirements*, 63 Fed. Reg. 66378, 66383–84 (Dec. 1, 1998). More recently, the FDA has had occasion to take the opposite position. Brief of Amicus Curiae United States, *Motus v. Pfizer, Inc.*, 358 F.3d 659 (9th Cir. 2004) (Nos. 02-55372, 02-55498) (urging the court to affirm summary

judgment because FDA regulations preempted plaintiff's duty to warn claim).

The perception of the administrative agency that its work is obstructed is not the standard at issue. Cf. *INS v. Cardoza-Fonseca*, 480 U.S. 421 (1987); *Chevron U.S.A., Inc. v. Nat. Resources Def. Council*, 467 U.S. 837 (1984) (rejecting outright deference to an agency's statutory interpretation in favor of an analysis of congressional intent and traditional statutory construction). It is only the intention of Congress that matters. See *Jones*, 430 U.S. at 525. Many agencies may believe that they possess comprehensive expertise in their field and that any requirement of law arising from another source interferes with their work.

Some tension between the FDA and common law tort remedies is natural, inevitable, and probably healthy. The two sources of law function to meet very different concerns. The tort process does not propose to provide policy and rules applicable to the entire pharmaceutical industry. Instead, it is concerned with compensating individuals for wrongs and providing pressure to curb negligent behavior and the sale of defective products. The FDA regulatory process does not propose to provide compensation in individual cases. Instead, it seeks to provide rules concerning testing, developing and labeling of pharmaceutical drugs which apply to all companies.

The record in this case does not indicate that the work of the FDA has been obstructed by the potential exposure of the manufacturer to state law tort liability. The evidence in this case is that a concern about inadvertent intra-arterial injection

surfaced by 1979 and was the subject of a relatively mild warning proposed by the defendant in 1981 and again in 1988. The FDA rejected the proposed labeling change 9 years later in 1997 in a brief comment. There is no evidence in this record that either the FDA or the manufacturer gave more than passing attention to the issue of whether to use an IV infusion to administer the drug. The proposed labeling change did not address the use of a free-flowing IV bag. Viewing the matter in hindsight through the lens of a single catastrophic case, this Court heard little evidence that the FDA reviewed the issue of the intravenous administration of Phenergan with scientific rigor or any sense of urgency.

This record is very different from the type of intensive regulation described by the Justice Department in their brief submitted in a May 2004 medical device case (*Horn v. Thoratec*). Ex. A to Wyeth's Memo dated 4/16/04. In that brief, the government described a comprehensive pre-market approval process for medical devices requiring an average of 1,200 hours of review time by the agency, thousands of pages of documentation, and substantial give-and-take between the agency and the manufacturer. Brief at p. 8, 21. According to the Justice Department, revision of an existing PMA follows an equally stringent and rigorous process. That is a very different process from the leisurely course of review for the Phenergan label changes conducted over some sixteen years. The regulatory process in this case was marked by long periods of dormancy and a conclusory decision in 1997 to require no change to the existing label. The recommendation of administration through a free-flowing IV bag never appears in the regulatory record. In short, a tort case is unlikely to obstruct the regulatory process when the

record shows that the FDA has paid very little attention to the issues raised by the parties at trial.

The principal basis for obstruction advanced by proponents of implied preemption in the pharmaceutical field is concern that excessive or unwarranted warnings will reduce the use of a safe and valuable medication. See Justice Department Brief in *Horn v. Thoratec* at 25–26; R. Pear, *In a Shift, Bush Moves to Block Medical Suits*, N.Y. Times, July 25, 2004, available at *http://www.nytimes.com/2004/07/25/politics/25DRUG.html*. The problem of "defensive warning" is not strong in this case. Any warning or instruction about the greater safety of a free-flowing IV bag relates only to the method of administration, not to the decision to use Phenergan. This case is different from cases involving proposed warnings of remote side effects which might dissuade physicians from using the drug to the detriment of the patient population.

There is no basis in this case to conclude that the work of the FDA was obstructed in any way by the indirect pressure of state law tort liability.

Conflict Preemption – Direct Conflict

The FDA regulations and a state law failure-to-warn case do not conflict directly. Compliance with the FDA labeling regulations is not a complete defense, but the manufacturer is entitled to raise it as a defense as defendant has done in this case. Restatement (Third) of Torts: Product Liability § 4. The record in this case is mixed concerning the ability of the defendant to provide a sharper warning about the risks

of intravenous injection. While the defendant insisted that severe sanctions, including criminal prosecution, would follow any change to the label as approved by the FDA in 1981 and 1997, the FDA regulations permit strengthened warnings without approval on an interim basis. 21 C.F.R. 314.70; see also *Kurer v. Parke, Davis & Co.*, 679 N.W. 2d 867, 872–74 (Wis. App. 2004).

More fundamentally, compliance with federal regulation does not provide a complete defense against tort liability. In a three-member partially dissenting opinion in *Cipollone v. Liggett Group*, 505 U.S. 504 (1992), Justice Blackman wrote:

> The effect of tort law on a manufacturer's behavior is necessarily indirect. Although an award of damages by its very nature attaches additional consequences to the manufacturer's continued unlawful conduct, no particular course of action (*e.g.*, the adoption of a new warning label) is required. A manufacturer found liable on, for example, a failure-to-warn claim may respond in a number of ways. It may decide to accept damages awards as a cost of doing business and not alter its behavior in any way. Or, by contrast, it may choose to avoid future awards by dispensing warnings through a variety of alternative mechanisms, such as package inserts, public service advertisements, or general educational programs. The level of choice that a defendant retains in shaping its own behavior distinguishes the indirect regulatory effect of the common law from positive enactments such as

> statutes and administrative regulations. Moreover, tort law has an entirely separate function – compensating victims – that sets it apart from direct forms of regulation.

Id., 505 U.S. 536–37 (citations omitted). There is no direct conflict between the FDA regulatory process and the common law remedy. The record in this case was that there have been at least 20 reports of amputations similar to plaintiff's injury since the 1960s. Green, Tr. 216. The defendant has remained in compliance with the FDA regulations by retaining the same warning about the risks of intra-arterial injection for several decades. This warning may be insufficient – certainly this jury found it to be so – and the result is that on some occasions the defendant may pay compensation. This tension does not amount to a direct conflict with the FDA labeling requirements. "The reason why many courts find no preemption is that the FDA's drug labeling decisions impose only 'minimum' standards that are open to supplementation by state law through a jury's verdict enforcing a manufacturer's common law duty to warn." *Caraker*, 172 F. Supp. 2d at 1033. The record in this case of a slow and imperfect regulatory process illustrates why courts have consistently held that FDA regulation provides a minimum standard of safety.

This Court finds no basis for federal preemption on grounds of direct conflict.

Appendix B

II. Causation

Defendant seeks to attribute sole causation as a matter of law to the actions of Jessica Fisch, P.A. who continued to inject the Phenergan despite a statement from the plaintiff that the injection hurt. This argument raises factual issues which were argued to the jury and resolved in plaintiff's favor at trial.

First, there is a factual dispute about whether it was too late for Ms. Fisch to stop the injection if the burning sensation experienced by the plaintiff was the Phenergan entering an artery. Second, the defendant requested and received a detailed instruction on efficient intervening cause, which addressed the same issues raised in this motion. Third, and most importantly, warnings are almost never the *sole* cause of an injury. Injury occurs only after the warning combines with human conduct to produce at least two concurrent causes of the event. *Gilman v. Towmotor Corp.*, 160 Vt. 116, 119–20 (1992); see also Restatement (Third) of Torts: Product Liability § 2 cmt. m (foreseeability); *id.* at § 16 (increased harm due to product defect). The warning is read – or not – by some human actor who follows it – or not. If subsequent human action were enough to break the chain of causation, there would be no cause of action for failure-to-warn. Restatement (Third) of Torts: Products Liability § 17.

The plaintiff's claim is not that Ms. Fisch was without blame or fault. Rather, as this Court understands it from trial, the claim is that if Ms. Fisch and her supervising physician had been told of the risk of limb death and amputation, she would have administered Phenergan by a safer method than the

butterfly infusion set. In rejecting the defense of efficient intervening cause, the jury decided that any conduct by Ms. Fisch did not break the chain of causation. There is sufficient evidence from Ms. Fisch, Dr. Matthews, and Dr. Green to support the jury's conclusion. This evidence is principally the testimony from Dr. Matthews that he would never have permitted administration of Phenergan through direct injection at his clinic if he had known of the risks to the patient and the testimony from Dr. Green that use of a free-flowing IV bag or intramuscular injection are safer methods of administering the drug.

Plaintiff argued at trial that a safer method of administration would have greatly reduced the risk of injury from inadvertent arterial injection. The defendant argued that injection through the butterfly-infusion set remains an appropriate method of administration. The jury rejected this defense and accepted the plaintiff's version of the facts. The Court will not overturn the verdict on a factual issue when there is evidence to support the jury's conclusion.

III. Damages

Defendant seeks a new trial for damages on the grounds that the Court did not grant a present value instruction for general damages (non-economic damages), which resulted in an oversized general damages award ($5,000,000). No challenge is raised to the award of special damages (medical and rehabilitative expenses and lost income) in the amount of $2.4 million.

Appendix B

A. Present Value Instruction

In this case, the Court rejected defendant's request for an instruction that any award of future general damages should be reduced to present value. There were several reasons for this.

First, the defendant put on no proof or argument concerning how to reduce future pain and suffering to present value. Nor, of course, did plaintiff. Future *economic* damages were always reduced to present value by plaintiff's economist and were essentially conceded without challenge by defendant. See, e.g., *Girroir v. Carpenter*, 136 Vt. 290, 292 (1978); *Wolfe v. Mendel*, 84 N.W.2d 109, 111, 115 (Neb. 1957) ("Where an instruction does not prohibit or negative the computation of damages upon the basis of their present worth, it will not be assumed that the jury did not understand that it was to estimate the present value of future earnings lost."). The defense never proposed a method by which the jury could discount for prevailing interest rates while accounting for the effects of expected inflation. Even the 12% discount rate proposed in the post-trial briefs was not suggested.

The briefing on this motion illustrates the practical difficulties of instructing the jury in a meaningful fashion that they should reduce the award of future pain and suffering to present value. The lawyers have presented wildly different proposals and methodologies. The defendant proposes a simple discount rate based on 12% or 2%. It offered no economic opinion at trial.

Appendix B

On the evidentiary record alone, including closing arguments, there was an inadequate basis for a present value instruction on future pain and suffering.

Second, the majority view – starting with the Restatement (Second) of Torts § 913A cmt. a – is that the calculation of future general damages is too subjective to be subjected to economic analysis by a lay jury. *Flanigan v. Burlington N., Inc.*, 632 F.2d 880, 886 (8th Cir. 1980); *O'Byrne v. St. Louis Southwestern Ry. Co.*, 632 F.2d 1285, 1286 (5th Cir. 1980); *Taylor v. Denver & Rio Grande W. R.R.*, 438 F.2d 351, 353 (10th Cir. 1971) ("[T]he courts [have] held that the better reasoned authority supports the rule that future pain and suffering should not be reduced to current worth."); *United States v. Harue Hayashi*, 282 F.2d 599, 605–06 (9th Cir. 1960); *Texas & Pacific Railway Co. v. Buckles*, 232 F.2d 257, 264 (5th Cir. 1956); *Chicago & N.W. Ry. Co. v. Candler*, 283 F. 881, 885 (8th Cir. 1922) ("The arbitrariness and artificiality of such a method is so apparent that to require a jury to apply it would, we think, be an absurdity."); *Purdy v. Belcher Refining Co.*, 781 F.Supp. 1559, 1563 (S.D. Ala. 1992); *Hanson v. Reiss Steamship Company*, 184 F.Supp. 545, 552–53 (D.Del. 1960) (holding that allowances for future pain and suffering are not subject to reduction to present worth); *Sleeman v. Chesapeake & O. Ry. Co.*, 305 F.Supp. 33, 36 n.1 (W.D. Mich. Sep 09, 1969) vacated, 424 F.2d 547 (6th Cir. 1970); *Schirra v. Delaware, L. & W.R. Co.*, 103 F.Supp. 812, 824 (M.D.Pa. 1952); *Beaulieu v. Elliott*, 434 P.2d 665, 671–72, 676 (Alaska 1967); *Braddock v. Seaboard Air Line R.R.*, 80 So.2d 662, 666–68 (Fla. 1955); *Delva v. Value Rent-A-Car*, 693 So.2d 574, 578 (Fla.App. 1997); *Bagley v. Akins*, 138 S.E.2d 430, 431 (Ga.App. 1964); *Brant v. Bockholt*, 532

N.W.2d 801, 803–04 (Iowa 1995) (collecting cases); *Louisville & N.R. Co. v. Gayle*, 263 S.W. 763 (Ky. 1924); *Busch v. Busch Const., Inc.*, 262 N.W.2d 377, 397 (Minn. 1977); *Barlage v. The Place, Inc.*, 277 N.W.2d 193, 195 (Minn.Sup.Ct. 1979); *Dickerson v. St. Louis S.W. Ry.*, 697 S.W.2d 210, 212 (Mo.App.1985); *Ball v. Burlington N. R.R.*, 672 S.W.2d 358, 361 (Mo.App. 1984); *Porter v. Funkhouser*, 382 P.2d 216, 218–19 (Nev. 1963); *Friedman v. C&S Car Serv.*, 527 A.2d 871, 873–75 (N.J. 1987); *Bready v. Tipton*, 407 P.2d 194, 206 (Okla. 1965); *Yost v. West Penn. Ry. Co.*, 9 A.2d 368, 369–70 (Pa. 1939); *Missouri Pac. R.R. v. Handley*, 341 S.W.2d 203, 205 (Tex.Civ.App. 1960); *Borzea v. Anselmi*, 258 P.2d 796, 804 (Wyo. 1952); 22 Am. Jur.2d *Damages* § 999 ("[T]he generally accepted rule is that the award [for pain and suffering] is not to be thus reduced [to present worth]."); see also *Oliveri v. Delta S.S. Lines, Inc.*, 849 F.2d 742, 750–52 (2d Cir. 1988) (noting that the majority of state jurisdictions do not reduce future pain and suffering awards and criticizing the rule requiring reduction to present value); *Hogan v. Santa Fe Trail Transportation Co.*, 85 P.2d 28, 34–38 (Kan. 1938) (Wedell, J., dissenting) (collecting early cases); *McKenna v. State*, 492 N.Y.S.2d 805, 807 (1985).

Third, it would involve the Court and the jury in something of a charade to pretend that without expert guidance, the jurors are capable of running accurate present value calculations on general damage awards proposed during deliberations. Judges and lawyers are universally incapable of performing the discount calculations with or without a calculator and the tables of historic interest rates and inflationary factors. It is invariably the topic of expert

testimony by an economist, and then only on the elements of special damage such as lost income and future medical bills. As Professor Dobbs succinctly states the issue:

> The Rule requiring reduction to present value must be qualified in several ways. In the first place, viewed realistically, the plaintiff is often not required to put on proof or explanation how reduction is to take place, and if the jury only gets an instruction to make the reduction without any further explanation, the rule probably does not mean very much. Beyond this, there is the agreed limit to the rule that only pecuniary losses are reduced. Thus awards for future pain and suffering, or for the future loss of companionship or guidance, are made without reduction. Presumably this is because it would be futile and even misleading to compute mathematically a reduction on an award that could have no mathematical basis in the first place.

D. Dobbs, *Handbook on the Law of Remedies* § 8.7, at 574 (1st ed. 1973).

For this reason, the Vermont Supreme Court has limited *pre-judgment* interest to special damages. *Gilman*, 160 Vt. at 121; see also *Bull v. Pinkham Eng'g Assoc.*, 170 Vt. 450, 463–64 (2000); *Ulm v. FordMotor Co.*, 170 Vt. 281, 292–94 (2000); *Remes v. Nordic Group, Inc.*, 169 Vt. 37, 40–41 (1999); *Estate of Fleming v. Nicholson*, 168 Vt. 495, 501–03 (1998); *Winey v. William E. Dailey, Inc.*, 161 Vt. 129, 141 (1993); *Turcotte v. Estate of LaRose*, 153 Vt. 196, 198–200 (1989).

It would be uneven at best to eliminate pre-judgment interest on general damages while requiring a reduction for future awards. Cf. Restatement (Second) of Torts § 913A cmt. a (linking present worth valuations with § 912 and its prohibition on prejudgment interest for pain and suffering). The reasoning that it is

The Court will not grant a new trial on the basis of the jury charge on general damages.

B. Reasonableness of the general damage award

Defendant cites several Vermont verdicts ranging from $1 million to $3 million recorded between 1977 and 1999. Defendant argues that at $5 million for general damages, this verdict is too high. Defendant does not take issue with the award of $2.4 for special damages and did not challenge the proof on that issue at trial.

This Court will not remit or set aside the damages verdict because the damage award is reasonably supported by the proof at trial. *Dean v. Arena*, 141 Vt. 647, 650 (1981). Several factors support a high award for pain and suffering.

First, this was an extraordinary case. The defendant describes it as tragic, and the Court saw it the same way at trial. The proof of plaintiff's joy and commitment to music prior to the loss of her arm was very compelling. The immediate effects of the injury were horrific. The changes in plaintiff's life as a result of her injury are wide and deep. This was as bad an injury case as any court is likely to see. What made the case unusual was the way that the injury cut so directly

into the life of a musician. The evidence of plaintiff's suffering and the loss of her ability to play the guitar at a professional level was powerful and undisputed.

Second, the jury verdicts presented by defendant place this verdict at one end of a range of results in serious cases in Vermont. So far as it is possible to tell, this jury verdict is the largest to date in a personal injury case. The verdicts are necessarily incomplete because they do not include settlements. This information is available only at third-hand, but it is generally known within the Vermont legal community; over the course of the last 10 years, a few severe injury cases have settled for amounts in excess of the verdicts listed by defendant. In October 2002, the Lamoille Superior Court entered judgment in a case involving quadriplegia for $48,000,000 following a bench trial. *Perron v. Vt. Utility Serv. Inc.*, No. 154-8-01LeCv (Cashman, J., Oct. 2002). On April 8, 2004, the Addison Superior Court entered judgment for $2,345,764 after a damages hearing in a default case concerning a severe foot injury. *Hadvab v. Manning*, No. 121-6-03 Ancv, 8 Vt.TrialCt.Rep. 274 (Toor, J.) This Court does not rely on these results in any direct evidentiary fashion because the underlying facts are not available for comparison, but they do provide some indication that a $7.4 million dollar verdict is not an isolated event within our legal culture.

The standard for review of a damages award is whether the award is "entirely excessive" or "shocks the conscience." *Turgeon v. Schneider*, 150 Vt. 268, 274 (1988); *Newhall v. Central Vermont Hospital*, 133 Vt. 572, 576–77 (1975). This was a bad damages case. The defendant chose not to challenge the damages at trial. The verdict falls within a range of results

seen in recent years in our state. This Court finds that the verdict is reasonably supported by the evidence and is not excessive for purposes of Rule 50 or Rule 59(a).

CONCLUSION

Defendant's motion for judgment under Rule 50 or, in the alternative, for a new trial on damages is DENIED.

Dated: 7-30-04

s/ Geoffrey W. Crawford
Superior Court Judge

APPENDIX C — DECISION OF THE VERMONT SUPREME COURT FILED DECEMBER 11, 2006, DENYING REARGUMENT

VERMONT SUPREME COURT

DOCKET NO. 2004-384

NOVEMBER TERM, 2006

DIANA LEVINE

v.

WYETH*

APPEALED FROM:
WASHINGTON SUPERIOR

DOCKET NUMBER: 670-12-01 Wncv

ENTRY ORDER

In the above-entitled cause, the Clerk will enter:

Appellant has filed a timely motion for reargument of this Court's October 27, 2006 decision in the above matter. Insofar as appellant has failed to demonstrate that the Court overlooked or misapprehended points of law or fact that would have affected the result, the motion is denied. V.R.A.P. 40.

Appendix C

BY THE COURT:

s/ _____
Paul L. Reiber, Chief Justice

s/ _____
John A. Dooley, Associate Justice

s/ _____
Denise R. Johnson, Associate Justice

s/ _____
Walter M. Morris, Jr., District Judge,
Specially Assigned

s/ _____
Frederic W. Allen, Chief Justice (Ret.),
Specially Assigned

APPENDIX D — CONSTITUTIONAL PROVISION INVOLVED

United States Constitution
Article VI, Clause 2

This Constitution, and the Laws of the United States which shall be made in Pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.

APPENDIX E — 21 U.S.C. § 393

TITLE 21—FOOD AND DRUGS
CHAPTER 9—FEDERAL FOOD, DRUG, AND COSMETIC ACT
SUBCHAPTER IX—MISCELLANEOUS

Sec. 393. Food and Drug Administration

(a) In general

There is established in the Department of Health and Human Services the Food and Drug Administration (hereinafter in this section referred to as the "Administration").

(b) Mission

The Administration shall—

(1) promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner;

(2) with respect to such products, protect the public health by ensuring that—

(A) foods are safe, wholesome, sanitary, and properly labeled;

(B) human and veterinary drugs are safe and effective;

(C) there is reasonable assurance of the safety and effectiveness of devices intended for human use;

(D) cosmetics are safe and properly labeled; and

(E) public health and safety are protected from electronic product radiation;

(3) participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements; and

(4) as determined to be appropriate by the Secretary, carry out paragraphs (1) through (3) in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products.

(c) Interagency collaboration

The Secretary shall implement programs and policies that will foster collaboration between the Administration, the National Institutes of Health, and other science-based Federal agencies, to enhance the scientific and technical expertise available to the Secretary in the conduct of the duties of the

Appendix E

Secretary with respect to the development, clinical investigation, evaluation, and postmarket monitoring of emerging medical therapies, including complementary therapies, and advances in nutrition and food science.

(d) Commissioner

(1) Appointment

There shall be in the Administration a Commissioner of Food and Drugs (hereinafter in this section referred to as the "Commissioner") who shall be appointed by the President by and with the advice and consent of the Senate.

(2) General powers

The Secretary, through the Commissioner, shall be responsible for executing this chapter and for—

(A) providing overall direction to the Food and Drug Administration and establishing and implementing general policies respecting the management and operation of programs and activities of the Food and Drug Administration;

(B) coordinating and overseeing the operation of all administrative entities within the Administration;

(C) research relating to foods, drugs, cosmetics, and devices in carrying out this chapter;

(D) conducting educational and public information programs relating to the responsibilities of the Food and Drug Administration; and

(E) performing such other functions as the Secretary may prescribe.

(e) Technical and scientific review groups

The Secretary through the Commissioner of Food and Drugs may, without regard to the provisions of title 5 governing appointments in the competitive service and without regard to the provisions of chapter 51 and subchapter III of chapter 53 of such title relating to classification and General Schedule pay rates, establish such technical and scientific review groups as are needed to carry out the functions of the Administration, including functions under this chapter, and appoint and pay the members of such groups, except that officers and employees of the United States shall not receive additional compensation for service as members of such groups.

(f) Agency plan for statutory compliance

(1) In general

Not later than 1 year after November 21, 1997, the Secretary, after consultation with appropriate scientific and academic experts, health care professionals, representatives of patient and consumer advocacy groups, and the regulated industry, shall develop and publish in the Federal Register a

plan bringing the Secretary into compliance with each of the obligations of the Secretary under this chapter. The Secretary shall review the plan biannually and shall revise the plan as necessary, in consultation with such persons.

(2) Objectives of agency plan

The plan required by paragraph (1) shall establish objectives and mechanisms to achieve such objectives, including objectives related to—

(A) maximizing the availability and clarity of information about the process for review of applications and submissions (including petitions, notifications, and any other similar forms of request) made under this chapter;

(B) maximizing the availability and clarity of information for consumers and patients concerning new products;

(C) implementing inspection and postmarket monitoring provisions of this chapter;

(D) ensuring access to the scientific and technical expertise needed by the Secretary to meet obligations described in paragraph (1);

(E) establishing mechanisms, by July 1, 1999, for meeting the time periods specified in this chapter for the review of all applications and submissions described in subparagraph (A) and submitted after November 21, 1997; and

(F) eliminating backlogs in the review of applications and submissions described in subparagraph (A), by January 1, 2000.

(g) Annual report

The Secretary shall annually prepare and publish in the Federal Register and solicit public comment on a report that—

(1) provides detailed statistical information on the performance of the Secretary under the plan described in subsection (f) of this section;

(2) compares such performance of the Secretary with the objectives of the plan and with the statutory obligations of the Secretary; and

(3) identifies any regulatory policy that has a significant negative impact on compliance with any objective of the plan or any statutory obligation and sets forth any proposed revision to any such regulatory policy.

APPENDIX F — 21 U.S.C. § 355(a)-(e)

TITLE 21—FOOD AND DRUGS CHAPTER 9—
FEDERAL FOOD, DRUG, AND COSMETIC ACT
SUBCHAPTER V—DRUGS AND DEVICES
Part A—Drugs and Devices

Sec. 355. New drugs

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title. The applicant shall file with the application the patent number

and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).

(2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include—

> (A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is

seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c) of this section—

(i) that such patent information has not been filed,

(ii) that such patent has expired,

(iii) of the date on which such patent will expire, or

(iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(B) if with respect to the drug for which investigations described in paragraph (1)(A) were conducted information was filed under paragraph (1) or subsection (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

(3) Notice of opinion that patent is invalid or will not be infringed—

Appendix F

(A) Agreement to give notice.—An applicant that makes a certification described in paragraph (2)(A)(iv) shall include in the application a statement that the applicant will give notice as required by this paragraph.

(B) Timing of notice.—An applicant that makes a certification described in paragraph (2)(A)(iv) shall give notice as required under this paragraph—

> (i) if the certification is in the application, not later than 20 days after the date of the postmark on the notice with which the Secretary informs the applicant that the application has been filed; or
>
> (ii) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(C) Recipients of notice.—An applicant required under this paragraph to give notice shall give notice to—

(i) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(ii) the holder of the approved application under this subsection for the drug that is claimed by the patent or a use of which is claimed by the patent (or a representative of the holder designated to receive such a notice).

(D) Contents of notice—A notice required under this paragraph shall—

(i) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and

(ii) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

Appendix F

(4)(A) An applicant may not amend or supplement an application referred to in paragraph (2) to seek approval of a drug that is a different drug than the drug identified in the application as submitted to the Secretary.

(B) With respect to the drug for which such an application is submitted, nothing in this subsection or subsection (c)(3) of this section prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(5)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1) or under section 262 of title 42, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 262 of title 42 if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall

be prepared by the Secretary and made available to the sponsor or applicant upon request.

(C) Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—

> (i) with the written agreement of the sponsor or applicant; or
>
> (ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance division personnel unless such field or compliance division personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection or section 262 of title 42 (including all scientific and medical matters, chemistry, manufacturing, and controls).

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

(1) Within one hundred and eighty days after the filing of an application under subsection (b) of this section, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(A) approve the application if he then finds that none of the grounds for denying approval

specified in subsection (d) of this section applies, or

(B) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) of this section on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(2) If the patent information described in subsection (b) of this section could not be filed with the submission of an application under subsection (b) of this section because the application was filed before the patent information was required under subsection (b) of this section or a patent was issued after the application was approved under such subsection, the holder of an approved application shall file with the Secretary the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If the holder of an approved application could not file patent information under subsection (b) of this section because it

was not required at the time the application was approved, the holder shall file such information under this subsection not later than thirty days after September 24, 1984, and if the holder of an approved application could not file patent information under subsection (b) of this section because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the Secretary shall publish it.

(3) The approval of an application filed under subsection (b) of this section which contains a certification required by paragraph (2) of such subsection shall be made effective on the last applicable date determined by applying the following to each certification made under subsection (b)(2)(A) of this section:

> (A) If the applicant only made a certification described in clause (i) or (ii) of subsection (b)(2)(A) of this section or in both such clauses, the approval may be made effective immediately.
>
> (B) If the applicant made a certification described in clause (iii) of subsection (b)(2)(A) of this section, the approval may be made effective on the date certified under clause (iii).
>
> (C) If the applicant made a certification described in clause (iv) of subsection (b)(2)(A) of this section, the approval shall be made effective

immediately unless, before the expiration of 45 days after the date on which the notice described in subsection (b)(3) of this section is received, an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under paragraph (2) or subsection (b)(1) of this section before the date on which the application (excluding an amendment or supplement to the application) was submitted. If such an action is brought before the expiration of such days, the approval may be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under subsection (b)(3) of this section or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that—

> (i) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on—
>
> > (I) the date on which the court enters judgment reflecting the decision; or

(II) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed;

(ii) if before the expiration of such period the district court decides that the patent has been infringed—

(I) if the judgment of the district court is appealed, the approval shall be made effective on—

(aa) the date on which the court of appeals decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(bb) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed; or

(II) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under section 271(e)(4)(A) of title 35;

(iii) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective as provided in clause (i); or

(iv) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent has been infringed, the approval shall be made effective as provided in clause (ii). In such an action, each of the parties shall reasonably cooperate in expediting the action.

Appendix F

(D) Civil action to obtain patent certainty.—

(i) Declaratory judgment absent infringement action.—

(I) In general.—No action may be brought under section 2201 of title 28 by an applicant referred to in subsection (b)(2) of this section for a declaratory judgment with respect to a patent which is the subject of the certification referred to in subparagraph (C) unless—

(aa) the 45-day period referred to in such subparagraph has expired;

(bb) neither the owner of such patent nor the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brought a civil action against the applicant for infringement of the patent before the expiration of such period; and

(cc) in any case in which the notice provided under

paragraph (2)(B) relates to noninfringement, the notice was accompanied by a document described in subclause (III).

(II) Filing of civil action.—If the conditions described in items (aa), (bb), and as applicable, (cc) of subclause (I) have been met, the applicant referred to in such subclause may, in accordance with section 2201 of title 28, bring a civil action under such section against the owner or holder referred to in such subclause (but not against any owner or holder that has brought such a civil action against the applicant, unless that civil action was dismissed without prejudice) for a declaratory judgment that the patent is invalid or will not be infringed by the drug for which the applicant seeks approval, except that such civil action may be brought for a declaratory judgment that the patent will not be infringed only in a case in which the condition described in subclause (I)(cc) is applicable. A civil action referred to in this subclause shall be brought

in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(III) Offer of confidential access to application.—For purposes of subclause (I)(cc), the document described in this subclause is a document providing an offer of confidential access to the application that is in the custody of the applicant referred to in subsection (b)(2) of this section for the purpose of determining whether an action referred to in subparagraph (C) should be brought. The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the

restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under subsection (b)(2)(A)(iv) of this section and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement.

(ii) Counterclaim to infringement action.—

(I) In general.—If an owner of the patent or the holder of the approved

application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) of this section or this subsection on the ground that the patent does not claim either—

(aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) No independent cause of action.—Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

(iii) No damages.—An applicant shall not be entitled to damages in a civil action under clause (i) or a counterclaim under clause (ii).

Appendix F

(E)(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of another application for a drug for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted effective before the expiration of ten years from the date of the approval of the application previously approved under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in clause

(A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) of this section before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under subsection (b) of this section after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (b)(2)(A) of this section. The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (C) shall be extended by such amount of time (if any) which is required for seven and

one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) of this section for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of

reference or use from the person by or for whom the investigations were conducted.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailabilty[1] studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b) of this section for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

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1. So in original. Probably should be "bioavailability".

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection and for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted and which refers to the drug for which the subsection (b) application was submitted effective before the expiration of two years from September 24, 1984.

(4) A drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production

facility is necessary to ensure the safety or effectiveness of the drug.

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the

patent information prescribed by subsection (b) of this section; or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.

(e) Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under

the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) the patent information prescribed by subsection (c) of this section was not filed within thirty days after the receipt of written notice from the Secretary specifying the failure to file such information; or (5) that the application contains any untrue statement of a material fact: Provided, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application submitted under subsection (b) or (j) of this section with respect to any drug

under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (k) of this section or to comply with the notice requirements of section 360(k)(2) of this title, or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based.

APPENDIX G — 21 U.S.C. § 352(f)

TITLE 21—FOOD AND DRUGS
CHAPTER 9—FEDERAL FOOD, DRUG, AND COSMETIC ACT SUBCHAPTER V—DRUGS AND DEVICES
Part A—Drugs and Devices

Sec. 352. Misbranded drugs and devices

A drug or device shall be deemed to be misbranded—

* * *

(f) Directions for use and warnings on label

Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users, except that where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement. Required labeling for prescription devices intended for use in health care facilities or by a health care professional and required labeling for in vitro diagnostic devices intended for use by health care professionals or in blood establishments may be made available solely by electronic means, provided that the labeling complies with all applicable requirements of law, and that the manufacturer affords such users the opportunity to request the labeling in paper form, and after such request, promptly provides the requested information without additional cost.

APPENDIX H — PUB L. 87-781 SEC 202

PUBLIC LAW 87-781 - OCT. 10, 1962

EFFECT ON STATE LAWS

Sec. 202. Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law.

APPENDIX I — 21 C.F.R. § 314.70

§ 314.70 Supplements and other changes to an approved application.

(a) *Changes to an approved application.*

(1) The applicant notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about it in a supplement under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the application under paragraph (d) of this section.

(2) The holder of an approved application under section 505 of the act must assess the effects of the change before distributing a drug product made with a manufacturing change.

(3) Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report).

(4) The applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with paragraphs (b) and (c) of this section.

(5) Except for a supplement providing for a change in the labeling, the applicant must include in each supplement and amendment to a supplement providing for a change under paragraph (b) or (c) of this section a statement certifying that a field copy has been provided in accordance with § 314.440(a)(4).

(6) A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the cover letter.

(b) *Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).*

(1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

(2) These changes include, but are not limited to:

(i) Except those described in paragraphs (c) and (d) of this section, changes in the qualitative or quantitative formulation of the drug product, including inactive ingredients, or in the specifications provided in the approved application;

(ii) Changes requiring completion of studies in accordance with part 320 of this chapter to demonstrate the equivalence of the drug product to the drug product as manufactured without the change or to the reference listed drug;

(iii) Changes that may affect drug substance or drug product sterility assurance, such as changes in drug substance, drug product, or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation;

(iv) Changes in the synthesis or manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance;

(v) The following labeling changes:

(A) Changes in labeling, except those described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x) of this section;

(B) If applicable, any change to a Medication Guide required under part 208 of this chapter, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter.

Appendix 1

(vi) Changes in a drug product container closure system that controls the drug product delivered to a patient or changes in the type (e.g., glass to high density polyethylene (HDPE), HDPE to polyvinyl chloride, vial to syringe) or composition (e.g., one HDPE resin to another HDPE resin) of a packaging component that may affect the impurity profile of the drug product.

(vii) Changes solely affecting a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody for the following:

(A) Changes in the virus or adventitious agent removal or inactivation method(s);

(B) Changes in the source material or cell line; and

(C) Establishment of a new master cell bank or seed.

(viii) Changes to a drug product under an application that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting that application.

(3) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug product made using

a change under paragraph (b) of this section. Except for submissions under paragraph (e) of this section, the following information must be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The drug product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to assess the effects of the change;

(v) The data derived from such studies;

(vi) For a natural product, a recombinant DNA-derived protein/ polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section; and

(vii) For sterilization process and test methodologies related to sterilization process validation, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section.

(4) An applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement and its mailing cover should be plainly marked: "Prior Approval Supplement- Expedited Review Requested."

(c) *Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).*

(1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

(2) These changes include, but are not limited to:

(i) A change in the container closure system that does not affect the quality of the drug product, except those described in paragraphs (b) and (d) of this section; and

(ii) Changes solely affecting a natural protein, a recombinant DNA-derived protein/polypeptide or a complex or conjugate of a drug substance with a monoclonal antibody, including:

(A) An increase or decrease in production scale during finishing steps that involves different equipment; and

(B) Replacement of equipment with that of a different design that does not affect the process methodology or process operating parameters.

(iii) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement—Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement—Changes Being Effected."

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(5) The applicant must not distribute the drug product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

> (i) The change requires approval prior to distribution of the drug product in accordance with paragraph (b) of this section; or
>
> (ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information.

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

> (i) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;
>
> (ii) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled

amount of drug product or from one container closure system to another;

(iii) Changes in the labeling to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

(7) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

Appendix I

(d) *Changes to be described in an annual report (minor changes).*

(1) Changes in the drug substance, drug product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product must be documented by the applicant in the next annual report in accordance with § 314.81(b)(2).

(2) These changes include, but are not limited to:

(i) Any change made to comply with a change to an official compendium, except a change described in paragraph (c)(2)(iii) of this section, that is consistent with FDA statutory and regulatory requirements.

(ii) The deletion or reduction of an ingredient intended to affect only the color of the drug product;

(iii) Replacement of equipment with that of the same design and operating principles except those equipment changes described in paragraph (c) of this section;

(iv) A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form drug

product, without a change from one container closure system to another;

(v) A change within the container closure system for a nonsterile drug product, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium;

(vi) An extension of an expiration dating period based upon full shelf life data on production batches obtained from a protocol approved in the application;

(vii) The addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, or deletion of an alternative analytical procedure;

(viii) The addition by embossing, debossing, or engraving of a code imprint to a solid oral dosage form drug product other than a modified release dosage form, or a minor change in an existing code imprint;

(ix) A change in the labeling concerning the description of the drug product or in the information about how the drug product is supplied, that does not involve a change in the dosage strength or dosage form; and

(x) An editorial or similar minor change in labeling.

(3) For changes under this category, the applicant is required to submit in the annual report:

(i) A statement by the holder of the approved application that the effects of the change have been assessed;

(ii) A full description of the manufacturing and controls changes, including the manufacturing site(s) or area(s) involved;

(iii) The date each change was implemented;

(iv) Data from studies and tests performed to assess the effects of the change; and,

(v) For a natural product, recombinant DNA-derived protein/ polypeptide, complex or conjugate of a drug substance with a monoclonal antibody, sterilization process or test methodology related to sterilization process validation, a cross-reference to relevant validation protocols and/or standard operating procedures.

(e) *Protocols.* An applicant may submit one or more protocols describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, and potency of the drug

product as these factors may relate to the safety or effectiveness of the drug product. Any such protocols, if not included in the approved application, or changes to an approved protocol, must be submitted as a supplement requiring approval from FDA prior to distribution of a drug product produced with the manufacturing change. The supplement, if approved, may subsequently justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

(f) *Patent information.* The applicant must comply with the patent information requirements under section 505(c)(2) of the act.

(g) *Claimed exclusivity.* If an applicant claims exclusivity under § 314.108 upon approval of a supplement for change to its previously approved drug product, the applicant must include with its supplement the information required under § 314.50(j).

APPENDIX J — PREAMBLE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 314, and 601

[Docket No. 2000N–1269]
(formerly Docket No. 00N–1269) RIN 0910–AA94

Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

* * *

D. Comments on Product Liability Implications of the Proposed Rule

In the proposal, FDA requested comments on the product liability implications of revising the labeling for prescription drugs.

(Comment 12) In comments, some manufacturers expressed concerns that, by highlighting selected information from the FPI to the exclusion of information not highlighted, they make themselves more vulnerable to product liability claims. Some of these comments also stated that the Highlights limitation statement, which states that Highlights does not contain all the information needed to prescribe a

drug safely and effectively and that practitioners should also refer to the FPI, would not constitute an adequate legal defense in a case alleging failure to provide adequate warning of a drug's risks.

Based on the agency's research and analysis in developing the prototype labeling that was the basis for the proposed rule (see comment 2), the agency has concluded that a labeling format that includes Highlights is more effective than a format that omits Highlights. In response to the comments and as discussed in the response to comment 35, FDA has taken steps to enhance the prominence of the Highlights limitation statement. FDA believes the statement will be effective in reminding prescribers that the information in the Highlights should not be relied on exclusively in making prescribing decisions and that it is important to consult the more detailed information in the FPI. We also believe that this limitation statement will help to ensure that the labeling will be considered in its entirety in any product liability action. FDA acknowledges the comment's concerns and, as discussed more fully in response to comment 13, believes that under existing preemption principles such product liability claims would be preempted.

(Comment 13) Some comments stated that the new format requirements might have product liability implications for drugs that are not subject to the new requirements. These comments expressed concern that labeling in the old format might be characterized by plaintiffs as inferior to labeling in the new format and, as a result, could be used as evidence that a manufacturer did not provide adequate warnings. They requested that the agency state in the final rule that FDA

approval of labeling, whether it be in the old or new format, preempts conflicting or contrary State law, regulations, or decisions of a court of law for purposes of product liability litigation.

FDA believes that under existing preemption principles, FDA approval of labeling under the act, whether it be in the old or new format, preempts conflicting or contrary State law. Indeed, the Department of Justice (DOJ), on behalf of FDA, has filed a number of amicus briefs making this very point. In order to more fully address the comments expressing concern about the product liability implications of revising the labeling for prescription drugs, we believe it would be useful to set forth in some detail the arguments made in those amicus briefs. The discussion that follows, therefore, represents the government's long standing views on preemption, with a particular emphasis on how that doctrine applies to State laws that would require labeling that conflicts with or is contrary to FDA-approved labeling.

Under the act, FDA is the expert Federal public health agency charged by Congress with ensuring that drugs are safe and effective, and that their labeling adequately informs users of the risks and benefits of the product and is truthful and not misleading. Under the act and FDA regulations, the agency makes approval decisions based not on an abstract estimation of its safety and effectiveness, but rather on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling (21 U.S.C. 355(d)). FDA considers not only complex clinical issues related to the use of the product in study populations, but

also important and practical public health issues pertaining to the use of the product in day-to-day clinical practice, such as the nature of the disease or condition for which the product will be indicated, and the need for risk management measures to help assure in clinical practice that the product maintains its favorable benefit-risk balance. The centerpiece of risk management for prescription drugs generally is the labeling which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively. FDA carefully controls the content of labeling for a prescription drug, because such labeling is FDA's principal tool for educating health care professionals about the risks and benefits of the approved product to help ensure safe and effective use. FDA continuously works to evaluate the latest available scientific information to monitor the safety of products and to incorporate information into the product's labeling when appropriate.

Changes to labeling typically are initiated by the sponsor, subject to FDA review, but are sometimes initiated by FDA. Under FDA regulations, to change labeling (except for editorial and other minor revisions), the sponsor must submit a supplemental application fully explaining the basis for the change (§§ 314.70 and 601.12(f) (21 CFR 314.70 and 601.12(f))). FDA permits two kinds of labeling supplements: (1) Prior approval supplements, which require FDA approval before a change is made (§§ 314.70(b) and 601.12(f)(1)); and (2) "changes being effected" (CBE) supplements, which

may be implemented before FDA approval, but after FDA notification (§§ 314.70(c) and 601.12(f)(2)). While a sponsor is permitted to add risk information to the FPI without first obtaining FDA approval via a CBE supplement, FDA reviews all such submissions and may later deny approval of the supplement, and the labeling remains subject to enforcement action if the added information makes the labeling false or misleading under section 502(a) of the act (21 U.S.C. 352). Thus, in practice, manufacturers typically consult with FDA prior to adding risk information to labeling. As noted in response to comment 5, however, a sponsor may not use a CBE supplement to make most changes to Highlights.

Since the proposed rule was published, FDA has learned of several instances in which product liability lawsuits have directly threatened the agency's ability to regulate manufacturer dissemination of risk information for prescription drugs in accordance with the act. In one case, for example, an individual plaintiff claimed that a drug manufacturer had a duty under California State law to label its products with specific warnings that FDA had specifically considered and rejected as scientifically unsubstantiated.[4] In some of these cases, the court determined that the State law claim could not proceed, on the ground that the claim was preempted by Federal law,[5] or was not properly before the

4. *Dowhal* v. *SmithKline Beecham Consumer Healthcare*, 2002 Cal. App. LEXIS 4384 (Cal. Ct. App. 2002), reversed, 2004 Cal. LEXIS 3040 (Cal. April 15, 2004).

5. *E.g.*, *Ehlis* v. *Shire Richwood, Inc.*, 233 F. Supp. 2d 1189, 1198 (D.N.D. 2002), *aff'd on other grounds*, 367 F.3d 1013 (8th Cir. 2004).

court by operation of the doctrine of primary jurisdiction.[6] In some cases, however, the court has permitted the claim to proceed.[7]

State law actions can rely on and propagate interpretations of the act and FDA regulations that conflict with the agency's own interpretations and frustrate the agency's implementation of its statutory mandate. For example, courts have rejected preemption in State law failure-to-warn cases on the ground that a manufacturer has latitude under FDA regulations to revise labeling by adding or strengthening warning statements without first obtaining permission from FDA. (*See, e.g., Eve* v. *Sandoz Pharm. Corp.*, 2002 U.S. Dist. LEXIS 23965 (S.D. In. Jan. 28, 2002); *Ohler* v. *Purdue Pharma, L.P.*, 2002 U.S. Dist. LEXIS 2368 (E.D. La. Jan. 22, 2002); *Motus* v. *Pfizer Inc.*, 127 F. Supp.

6. *E.g., Bernhardt* v. *Pfizer, Inc.*, 2000 U.S. Dist. LEXIS 16963 (S.D.N.Y. Nov. 16, 2000). This doctrine allows a court to refer a matter to an administrative agency for an initial determination where the matter involves technical questions of fact and policy within the agency's jurisdiction. If a court finds that the agency has primary jurisdiction, the court stays the matter and instructs the plaintiff to initiate an action with the agency. *See, e.g., Israel* v. *Baxter Labs., Inc.*, 466 F.2d 272, 283 (D.C. Cir. 1972); see also 21 CFR 10.60.

7. *Dowhal* v. *SmithKline Beecham Consumer Healthcare*, 2002 Cal. App. LEXIS 4384 (Cal. Ct. App. 2002), *reversed*, 2004 Cal. LEXIS 3040 (Cal. April 15, 2004); *Bernhardt* v. *Pfizer, Inc.*, 2000 U.S. Dist. LEXIS 16963 (S.D.N.Y. November 16, 2000); *Motus* v. *Pfizer, Inc.*, 127 F. Supp. 2d 1085 (C.D. Cal. 2000), summary judgment granted, 196 F. Supp. 2d 984, 986 (C.D. Cal. 2001), aff'd, 2004 U.S. App. LEXIS 1944 (9th Cir. February 9, 2004); *In re Paxil Litigation*, 2002 U.S. Dist. LEXIS 16221 (C.D. Cal. August 16, 2002), transferred, 296 F. Supp. 2d 1374 (J.P.M.L. 2003).

2d 1085 (C.D. Cal. 2000); *Bansemer* v. *Smith Labs., Inc.*, 1988 U.S. Dist. LEXIS 16208 (E.D. Wis. Sept. 12, 1988); *McEwen* v. *Ortho Pharm Corp.*, 528 P.2d 522 (Ore. 1974).) In fact, the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act. A manufacturer may, under FDA regulations, strengthen a labeling warning, but in practice manufacturers typically consult with FDA before doing so to avoid implementing labeling changes with which the agency ultimately might disagree (and that therefore might subject the manufacturer to enforcement action).

Another misunderstanding of the act encouraged by State law actions is that FDA labeling requirements represent a minimum safety standard. According to many courts, State law serves as an appropriate source of supplementary safety regulation for drugs by encouraging or requiring manufacturers to disseminate risk information beyond that required by FDA under the act. (*See, e.g.*, *Brochu* v. *Ortho Pharm. Corp.*, 642 F.2d 652 (1st Cir. 1981); *Salmon* v. *Parke-Davis and Co.*, 520 F.2d 1359 (4th Cir. 1975); *Caraker* v. *Sandoz Pharm. Corp.*, 172 F. Supp. 2d 1018 (S.D. Ill. 2001); *Mazur* v. *Merck & Co., Inc.*, 742 F. Supp. 239 (E.D. Pa. 1990); *In re Tetracycline Cases*, 747 F. Supp. 543 (W.D. Mo. 1989).) In fact, FDA interprets the act to establish both a "floor" and a "ceiling," such that additional disclosures of risk information can expose a manufacturer to liability under the act if the additional statement is unsubstantiated or otherwise false or misleading. Given the comprehensiveness of FDA regulation of drug safety, effectiveness, and labeling under the act, additional requirements for the disclosure of risk information are not necessarily more protective of patients. Instead, they can erode and disrupt the careful and truthful

representation of benefits and risks that prescribers need to make appropriate judgments about drug use. Exaggeration of risk could discourage appropriate use of a beneficial drug.

State law requirements can undermine safe and effective use in other ways. In the preamble accompanying the proposal, FDA noted that liability concerns were creating pressure on manufacturers to expand labeling warnings to include speculative risks and, thus, to limit physician appreciation of potentially far more significant contraindications and side effects (65 FR 81082 at 81083). FDA has previously found that labeling that includes theoretical hazards not wellgrounded in scientific evidence can cause meaningful risk information to "lose its significance" (44 FR 37434 at 37447, June 26, 1979). Overwarning, just like underwarning, can similarly have a negative effect on patient safety and public health. (See section X of this document.) Similarly, State-law attempts to impose additional warnings can lead to labeling that does not accurately portray a product's risks, thereby potentially discouraging safe and effective use of approved products or encouraging inappropriate use and undermining the objectives of the act. (*See, e.g., Dowhal* v. *SmithKline Beecham Consumer Healthcare*, 2002 Cal. App. LEXIS 4384 (Cal. Ct. App. 2002) (allowing to proceed a lawsuit involving a California State law requiring warnings in the labeling of nicotine replacement therapy products that FDA had specifically found would misbrand the products under the act), reversed, 2004 Cal. LEXIS 3040 (Cal. April 15, 2004).)

State law actions also threaten FDA's statutorily prescribed role as the expert Federal agency responsible for

evaluating and regulating drugs. State actions are not characterized by centralized expert evaluation of drug regulatory issues. Instead, they encourage, and in fact require, lay judges and juries to second-guess the assessment of benefits versus risks of a specific drug to the general public—the central role of FDA—sometimes on behalf of a single individual or group of individuals. That individualized reevaluation of the benefits and risks of a product can result in relief—including the threat of significant damage awards or penalties—that creates pressure on manufacturers to attempt to add warnings that FDA has neither approved nor found to be scientifically required. This could encourage manufacturers to propose "defensive labeling" to avoid State liability, which, if implemented, could result in scientifically unsubstantiated warnings and underutilization of beneficial treatments.

FDA has previously preempted State law requirements relating to drugs in rulemaking proceedings. For example:

• In 1982, FDA issued regulations requiring tamper-resistant packaging for OTC drugs. In the preamble accompanying the regulations, FDA stated its intention that the regulations preempt any State or local requirements that were "not identical to * * * [the rule] in all respects" (47 FR 50442 at 50447, November 5, 1982).

• In 1986, FDA issued regulations requiring aspirin manufacturers to include in labeling a warning against use in treating chicken pox or flu symptoms in children due to the risk of Reye's Syndrome. In the accompanying preamble, FDA said the regulations preempted "State and local

packaging requirements that are not identical to it with respect to OTC aspirin-containing products for human use" (51 FR 8180 at 8181, March 7, 1986).

• In 1994, FDA amended 21 CFR 20.63 to preempt State requirements for the disclosure of adverse event-related information treated as confidential under FDA regulations (59 FR 3944, January 27, 1994). (See also 47 FR 54750, December 3, 1982) ("FDA believes that differing State OTC drug pregnancy-nursing warning requirements would prevent accomplishment of the full purpose and objectives of the agency in issuing the regulation and that, under the doctrine of implied preemption, these State requirements are preempted by the regulation as a matter of law.")

As noted previously, DOJ has made submissions to courts in a number of cases in which private litigants asserted a State law basis for challenging the adequacy of risk information provided by manufacturers for drugs in accordance with FDA requirements under the act. In each case, DOJ argued that the doctrine of preemption precluded the plaintiff's claim from proceeding.[8] The practice of

8. The DOJ submissions in these cases relied on the doctrine of implied preemption or primary jurisdiction. Although the act itself contains no general express pre-emption provision for drugs, a provision of legislation amending the drug provisions addresses the relationship of the legislation to State law. Section 202 of the Drug Amendments of 1962 (Public Law 87-781, Title II, section 202, 76 Stat. 793 (October 10, 1962)) provides: "Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would

(Cont'd)

addressing conflicting State requirements through participation in litigation (including product liability cases) in which the Government is not a party is not new. For example, DOJ participated on FDA's behalf in favor of pre-emption in *Jones* v. *Rath Packing Company*, 430 U.S. 519 (1977), *Grocery Manufacturers of America, Inc.* v. *Gerace*, 755 F.2d 993 (2d Cir. 1985), *Eli Lilly & Co., Inc.* v. *Marshall*, 850 S.W.2d 155 (Tex. 1993), and *Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 352–53 (2001). FDA believes that State laws conflict with and stand as an obstacle to achievement of the full objectives and purposes of Federal law when they purport to compel a firm to include in labeling or advertising a statement that FDA has considered and found scientifically unsubstantiated. In such cases, including the statement in labeling or advertising would render the drug misbranded under the act (21 U.S.C. 352(a) and (f)). The agency believes that State law conflicts with and stands as an obstacle to achievement of the full objectives and purposes of Federal law if it purports to preclude a firm from including in labeling or advertising a statement that is included in prescription drug labeling. By complying with the State law in such a case and removing the statement from labeling, the firm would be omitting a statement required under § 201.100(c)(1) as a condition on the exemption from the requirement of adequate directions for use, and the omission

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(Cont'd)

be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law." The existence of a legislative provision addressing pre-emption does not bar the operation of ordinary principles of implied preemption (*Geier* v. *American Honda Motor Co., Inc.*, 529 U.S. 861, 869 (2000)).

would misbrand the drug under 21 U.S.C. 352(f)(1). The drug might also be misbranded on the ground that the omission is material within the meaning of 21 U.S.C. 321(n) and makes the labeling or advertising misleading under 21 U.S.C. 352(a) or (n).

Consistent with its court submissions and existing preemption principles, FDA believes that at least the following claims would be preempted by its regulation of prescription drug labeling. (1) Claims that a drug sponsor breached an obligation to warn by failing to put in Highlights or otherwise emphasize any information the substance of which appears anywhere in the labeling; (2) claims that a drug sponsor breached an obligation to warn by failing to include in an advertisement any information the substance of which appears anywhere in the labeling, in those cases where a drug's sponsor has used Highlights consistently with FDA draft guidance regarding the "brief summary" in direct-to-consumer advertising ("Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements," 69 FR 6308 (February 2004)) (see comment 112); (3) claims that a sponsor breached an obligation to warn by failing to include contraindications or warnings that are not supported by evidence that meets the standards set forth in this rule, including § 201.57(c)(5) (requiring that contraindications reflect "[k]nown hazards and not theoretical possibilities") and (c)(7); (4) claims that a drug sponsor breached an obligation to warn by failing to include a statement in labeling or in advertising, the substance of which had been proposed to FDA for inclusion in labeling, if that statement was not required by FDA at the time plaintiff claims the sponsor had an obligation to warn (unless FDA has made a finding that the sponsor withheld material information relating to the proposed warning

before plaintiff claims the sponsor had the obligation to warn); (5) claims that a drug sponsor breached an obligation to warn by failing to include in labeling or in advertising a statement the substance of which FDA has prohibited in labeling or advertising; and (6) claims that a drug's sponsor breached an obligation to plaintiff by making statements that FDA approved for inclusion in the drug's label (unless FDA has made a finding that the sponsor withheld material information relating to the statement). Preemption would include not only claims against manufacturers as described above, but also against health care practitioners for claims related to dissemination of risk information to patients beyond what is included in the labeling. (See, e.g., *Bowman* v. *Songer*, 820 P.2d 1110 (Col. 1991).)

FDA recognizes that FDA's regulation of drug labeling will not preempt all State law actions. The Supreme Court has held that certain State law requirements that parallel FDA requirements may not be preempted (*Medtronic, Inc.* v. *Lohr*, 518 U.S. 470, 495 (1996) (holding that the presence of a State law damages remedy for violations of FDA requirements does not impose an additional requirement upon medical device manufacturers but ''merely provides another reason for manufacturers to comply with * * * federal law''); id. at 513 (O'Connor, J., concurring in part and dissenting in part); id)). *But see Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 352–53 (2001) (holding that "fraud on the FDA" claims are preempted by Federal law); 21 U.S.C. 337(a) (restricting the act enforcement to suits by the United States); *In re Orthopedic Bone Screw Prods. Liability Litig.*, 159 F.3d 817, 824 (3d Cir. 1998) (''Congress has not created an express or implied private cause of action for violations of the FDCA or the MDA [Medical Device Amendments]'').

* * * *

APPENDIX K — REGULATORY HISTORY

INTERNAL CORRESPONDENCE

William E. Langeland, Ph.D.

Company WLD located Radnor

Subject Phenergan® Advere Reaction
Lt. Colonel Harry Cerha
Headquarters, AFMSTC
Washington, D.C. 20333

From Walter H. Comer, M.D.

Company WLD located Radnor

Date February 17, 1967

Dear Bill:

Lt. Colonel Harry Cerha informed us of an adverse reaction occurring in a woman during labor involving three drugs given intravenously in a single injection. These drugs are Demerol®, Leritine® and Phenergan. A severe arteriospasm resulted during the injection, with pain and cyanosis observed in the arm. In spite of recognized, acceptable treatment, the spasm continued, resulting in gangrene of the arm and subsequent amputation.

The information from Colonel Cerha was given in a phone conversation February 15, 1967, and is not complete. The incident occurred some time in 1965. This information is being presented to the Food and Drug Administration

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because it is the first such incident reported to us involving Phenergan.

Phenergan was given (50 mg.) IV in a dose not recommended in the approved Phenergan direction circular. The direction circular also gives warning against perivascular extravasation and also includes a warning against intra - arterial injection.

Information reached us because of an allegation on the part of the patient against the Air Force.

Sincerely,

s/ Walter H. Comer
Walter H. Comer, M.D.

WHC: jda

Enclosure – Drug Reaction Report

Appendix K

DEPARTMENT OF HEALTH, EDUCATION,
AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND

NDA 8-857/S-005

Wyeth Laboratories
Attention: Earl T. Lewis, M.D.
P. O. Box 8299
Philadelphia, Pennsylvania 19101 May 4, 1976

Gentlemen:

Reference is made to your supplemental new drug application of November 14, 1975 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for PHENERGAN® (promethazine hydrochloride) Injection.

The supplemental application provides for a revised package insert as discussed in our conference of August 25, 1975 and in our letter of August 29, 1975.

We have completed review of this supplemental application as submitted with draft labeling. In order to furnish adequate information for the safe use of the drug, the following revisions in the labeling should be made:

* * *

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D. WARNINGS

* * *

5. The last paragraph as it appears on page three of the draft labeling should be modified as follows: the statement "when used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg per cc. and at a rate not too exceed 25 mg per minute," should be deleted and removed to the DOSAGE AND ADMINISTRATION section. Preceding the remainder of the paragraph the following statement should appear, all in caps: "ASPIRATION OF DARK BLOOD DOES NOT PRECLUDE INTRA-ARTERIAL NEEDLE PLACEMENT AS BLOOD IS DISCOLORED UPON CONTACT WITH PROMETHAZINE." The remainder of the paragraph is acceptable.

* * *

F. ADVERSE REACTIONS:

* * *

2. The paragraph entitled "Cardiovascular Effects" should be revised. This paragraph should be rewritten as follows: "Postural hypotension is the most common

cardiovascular effect of promethazine. Reflex tachycardia associated with mild increases in blood pressure have been seen with the use of promethazine hydrochloride. Bradycardia, faintness, dizziness and EKG changes, including blunting of T waves and prolongation of the Q-T INTERVAL may be seen. INTERARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY."

* * *

Please submit your revised labeling in draft form for our review.

Sincerely yours,
Margaret A. Clark, M.D.
Director
Division of Surgical-Dental
Drug Products
Bureau of Drugs

Appendix K

FOOD AND DRUG ADMINISTRATION
BUREAU OF DRUGS
ANESTHESIOLOGY ADVISORY COMMITTEE
EIGHTEENTH MEETING

October 14, 1976

Teakwood Suite
The San Francisco Hilton
Mason and O'Farrell Streets
San Francisco, California

MEMBERS OF THE ADVISORY COMMITTEE PRESENT:

Betty J. Ramforth, M.D. - Chairman
Philip R. Bromege, M.S.
Burnell R. Brown, Jr., M.D., Ph.D.
Helmut F. Cascorbi, M.D., Ph.D.
Athole G. Jacobi, M.D.
Kenneth Sugioka, M.D.

MEMBERS OF THE ADVISORY COMMITTEE ABSENT:

M. Robert Knapp, M.D.

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BUREAU OF DRUGS PERSONNEL IN ATTENDANCE:

Gerald M. Rachanow, Executive Secretary
Margaret A. Clark, M.D., HFD-160
Patricia H. Russell, M.D., HFD-160
David L. Scally, M.D., HFD-160

PUBLIC ATTENDEES:

Jeffrey M. Baden - Stanford, California
Harold H. Borgstodt, M.D. - Rochester, New York
Terrell A. Crowley, Ph.D. - North Chicago, Illinois
Edmond I. Eger, II, M.D. - San Francisco, California
Louis L. Ferstandig, Ph.D. - Hackensack, New Jersey
Ben Hitt, Ph.D. - Stanford, California
Duncan A. Holaday, M.D. - Miami, Florida
John B. Jewell, M.D. - New York, New York
Richard I. Mazze, N.D. - Stanford, California
James L. McNahon - New York, New York
William A. Hischel - Lexington, Massachusetts
W. D. Northcroft - San Mateo, California
James L. Ryan - Santa Ana, California
Charles W. Simons - Lexington, Massachusetts
Bradley E. Smith, M.D. - Nashville, Tennessee
Ross C. Terrell - New Providence, New Jersey
James F. Vitcha - Cape Coral, Florida

ANESTHESIOLOGY ADVISORY COMMITTEE

The meeting was called to order at 9:00 A.M., Dr. Betty J. Bamforth, Chairman, presiding. Dr. Athole G. Jacobi, the newest Committee member, was introduced.

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OPEN PUBLIC HEARING:

An opportunity was provided for members of the public present to make comments or ask questions relevant to the Advisory Committee's agenda or other work, and no comments or questions were presented.

OPEN COMMITTEE DISCUSSION:

* * *

The second item on the agenda was the proposed package insert revision for Phenergan (promethazine hydrochloride) Injection, NDA 8-857, The FDA has proposed that the first paragraph of the CONTRAINDICATIONS section of the package insert be revised to state: "Promethazine is contraindicated in comatose states, in patients who have received large amounts of central nervous system depressants (alcohol, barbiturates, narcotics, etc.), in patients who have bone marrow depression, and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine." The manufacturer, Wyeth Laboratories, disagrees with the contraindication to the use of Phenergan Injection in bone marrow depression. The question presented to the Advisory Committee was whether "Based on the limited case reports of blood dyscrasias which have been received, should the use of Phenergan Injection be contraindicated in bone marrow depression? or would a WARNING statement be more appropriate at this time?" The Committee agreed that present evidence does not warrant a contraindication, but that it certainly warrants a warning.

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The FDA medical officer had suggested that since arterial injection is not an acceptable means of administering drugs that the second paragraph of the CONTRAINDICATIONS section (concerning intra-arterial injection) be deleted. Wyeth Laboratories has stated its strong feeling that this contraindication to the intra-arterial injection of Phenergan is entirely appropriate in its present location and is essential to ensure the safe use of this drug. The question presented to the Advisory Committee was "Should the reference to intra-arterial injection remain or be deleted from the CONTRAINDICATIONS section?" The Committee agreed that it had no objections to including this statement under CONTRAINDICATIONS and that, because of the seriousness of the problem, statements concerning intra-arterial injection which appear in the WARNINGS section should remain there also.

One of the Committee members commented that the present statement (i.e., Subcutaneous injection is not recommended; . . .) concerning subcutaneous injection was pretty mild and that this statement should be made stronger or should appear in the CONTRAINDICATIONS section because there have been at least three or four cases of abscesses developing because of subcutaneous injection of the drug. He added that tissue necrosis and slough may follow subcutaneous injection and that the drug should be given by deep intra-muscular injection. The Committee agreed that an additional paragraph should be added to the CONTRAINDICATIONS section stating that Phenegan Injection should not be given by subcutaneous injection (because of the possibility of

abscesses developing and of tissue necrosis) and that deep intra-muscular injection is the recommended route of administration of the drug.

* * *

The Committee was also asked: "Since it appears that it may be difficult to aspirate or be aware of intra-arterial pressure when using Wyeth's Tubex system to administer this drug and that more intra-arterial injections occur when the Tubex system is used is used in place of a plain needle and syringe, should the use of Tubex be discussed in this section (or perhaps in the PRECAUTIONS section)?" The Committee agreed that the following statement should be added under the Parenteral Administration subsection of the WARNINGS section: "If a Tubex system is used for intravenous injection, the drug should be injected into a satisfactorily functioning intravenous set."

* * *

The next meeting was tentatively scheduled for March 1977. The meeting adjourned at 2:45 P.M.

I certify that I attended the eighteenth meeting of the Anesthesiology Advisory Committee of the Food and Drug Administration cn October 14, 1976, and that these minutes accurately reflect what transpired.

Appendix K

Chairman s/ Betty J. Bamforth
Betty J. Bamforth, M.D.

Executive Secretary s/ Gerald K. Rachanow
Gerald M. Rachanow

Appendix K

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 26, 1987

NDA 8-957/5-009

Wyeth Laboratories
P.O. Box 8299
Philadelphia, PA 19101

Attention: Paul V. Uses
Associate Director
Drug Regulatory Affairs

Gentlemen:

Please refer to your supplemental new drug application dated September 21, 1981 (S-009) submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Phenegan (promthazine HCl) Injection.

The supplemental application provides for revised labeling to conformance with the Labeling Format Revision Program (21 CFR 201.56 and 201.57).

Reference is also made to the agency letter dated November 5, 1984, requesting further revisions in the labeling. We have

not yet received a response to the referenced letter. The following comments, most of which were conveyed to you by Dr. D. Scally, should be incorporated in the revised labeling. Please note that the comments include some deficiencies which were noted in S-012 dated November 13, 1986, as well as those noted in the original labeling supplement dated September 21, 1981.

The labeling should be revised as follows:

* * *

WARNINGS

Please revise your WARNINGS discussion of Inadvertent Intra-arterial Injection according to the following text:

> "INADVERTENT INTRA-ARTERIAL INJECTION: There are reports of necrosis leading to gangrene, requiring amputation, following injection of promethazine, usually in conjunction with other drugs; the intravenous route was intended in these cases, but arterial or partial arterial placement of the needle is now suspect. The mechanism is uncertain, however, animal experiments with other arteriolar irritants suggests that the initiating factor may be platelet aggregation and thrombosis starting distal to the site of injection.
>
> "The first sign may be the patient's reaction to a sensation of fiery burning, roughly following the

distribution path of the injected artery; no more drug should be injected until the situation is remedied. Blanching may be present early, may be transient or may not be noted at all. Blotchy dynosis and dark discoloration usually follows.

"There is no established treatment other than prevention:

1. Beware of the close proximity of arteries and veins at commonly used injection sites and consider the possibility of aberrant arteries.

2. When used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg/ml and at a rate not to exceed 25 mg/minute. Injection through a properly running intravenous infusion may enhance the possibility of detecting arterial placement. In addition, this results in delivery of a lower concentration of any arteriolar irritant.

3. Subcutaneous swelling near the site of injection calls for discontinuation of promethazine administration and reevaluation of the situation. This sign may be

indicative of venous extravasion, which may result in localized necrosis, or it may signify partial arterial placement of needle or catheter.

4. Beware *that the characteristic bright-red color of arterial blood is discolored by contact with promethazine.* (Italics or different print underlined.)

"Post injury injection of vasodilators an/or arterial infusion of parenteral fluids are generally regarded as being of no value in altering outcome. Animal experiments and published individual case reports concerned with a variety of arteriolar irritants suggests that one or more of the following *may* be a benefit in reducing the area of necrosis:

1. Arterial injection of heparin at the site of injury, followed by systemic anticoagulation.

2. Sympathetic blood (or brachial plexus block in the arm), if anticoagulant therapy permits.

3. Intra-arterial gluocorticoid injection at the site of injury, followed by systemic steroids.

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4. A recent case report (non-promethazine drug injury) suggests that intra-arterial urokinase may promote fibrinolysis, even if administered late in treatment."

The references supporting the above discussion are:

1. G.S. Buckspan, et al., Intraarterial Drug Injury: Studies of Etiology and Potential Treatment. JL. SURG. RES. 24(4): 294-301, 1978.

2. W.P. Wiedeman, et al., *In Vivo* Microscopic Observations of Intra-Arterial Injections of Barbiturates, JL. SURG. RES. 22(2): 94-108, 1977.

3. S.S. Brown, et al., Intra-Arterial Barbiturates, BRIT. JL. ANAES. 40: 13-19, 1968.

4. J.S. Mathers & E. Goodhead, Intra-arterial Methohexitone and Thiopentone, ANAESTHESIA 21(1): 81-89, 1966.

5. G.A. Webb & N. Lampert, Accidental Arterial Injections. AM. J. OBST. & GYNEC. 101(3): 365-371, 1 June 1968.

6. H.S. Engler, et al., Production of Gangrenous Extremeties by Intra-Arterial Injections, AMERICAN SURGEON 30(9): 602-607, Sept. 1964.

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7. D.L. Hager & J.N. Wilson, Gangrene of the Hand Following Intra-Arterial Injection, ARCH. SURG. 94: 86-89, Jan. 1967.

8. R.F. Lynas & W.I.K. Bisset, Intra-Arterial Thiopentone, ANAESTHESIA 24(2): 257-261, April 1969.

9. G. Corser, et al., Ischamia Following Self Administered Intra-Arterial Injection of Methylphenidate and Diamorphine, ANAESTHESIA 40: 51-54, 1985

10. D.J. Waters, Intra-Arterial Thiopental, ANAESTHESIA 21(3): 346-356, July 1966.

11. Correspondence Regarding Thiopental and Thiamylal (3 Letters): 1. L.C. Mark, 2. J.W. Dundee, 3. S. Dohi & M. Naito. ANESTHESIOLOGY 59: 153-155, 1983.

12. D. Albo, K. Reemtsma, et al., Effect of Intra-Arterial Injections of Barbiturates, AMERICAN JL. OF SURGERY 120: 676-678, November 1970.

13. E.C. Klatte, et al., Toxicity of Intra-Arterial Barbiturates and Tranquilizing Drugs, RADIOLOGY 92(4) 92(4): 700-704, March 1969.

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14. M.L. Nahrwold, et al., Inadvertent Intra-Arterial Injection of Mephenteramine, ROCKY MOUNTAIN MEDICAL JOURNAL, 70(9): 38-39, September 1973.

15. G. Enloe, et al., Hazards of Intra-Arterial Injection of Hydroxyzine, CANADIAN ANAES. SOC. JL. 16(5): 425-428, September 1969.

16. H.S. Engler, et al., Gangrenous Extremities Resulting from Intra-Arterial Injections, ARCH. SURG. 94: 644-651, May 1967.

17. J.B. Kinmonth & R.C. Shephard, Accidental Injection of Thiopentone Into Arteries, Studies of Pathology and Treatment, BRITISH MEDICAL JOURNAL, 2: 914-918, 1959.

18. D. Goldsmith & N. Trieger, Accidental Intra-Arterial Injection: A Medical Emergency, ANESTHESIA PROGRESS 226): 180-183, Nov.-Dec. 1975.

19. R. Miller, et al., Intra-Arterial Injection of a Barbiturate — A Case Report, ANESTHESIA PROGRESS 23(1): 25-27, Jan.-Feb. 1976.

20. H.H. Stone & C.C. Donnelly, REVIEW ARTICLE, The Accidental Intra-Arterial Injection of Thiopental, ANESTHESIOLOGY 22: 995-1006, 1961.

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* * *

Please submit revised draft labeling as soon as possible.

Sincerely yours,
s/ [illegible]
Patricia H. Russell, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

Appendix K

CONFIDENTIAL

WYETH
AYERST

INTERNAL CORRESPONDENCE

to: File
from: James O'Shaughnessy
company: W-AR located 170/2
subject: Phenergan® Injection Pending Supplements
date: January 30, 1997

On January 29, 1997, I spoke with Ms. Beverly Gallauresi of the Division of Pulmonary Drug Products (DPDP) regarding the following pending supplemental applications for Phenergan Injection.

NDA No. 8-857/S-009
Labeling Supplement

This supplement was initially filed in 1981. There have been numerous amendments and submissions of draft labeling and supportive documentation over the years. In June 1996, Wyeth-Ayerst was asked to prepare a narrative outlining the differences in the text of the currently approved package insert and any text changes since 1992. During the remainder of 1996, the DPDP consistently advised that the labeling review was nearing an end.

During today's conversation, Ms. Gallauresi indicated that the labeling review is complete. However, because it has taken the DPDP so long to complete the review, they are

taking extra care to make sure they have dotted every "i" and crossed every "t." She advised me that a letter is circulating within the DPDP for final review and comments. Ms. Gallauresi said she hoped this letter could be FAXed to us in the very near future, however, she could not guarantee that this would happen before Friday, February 7, 1997.

Appendix K

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FEB 21 1997

CONFIDENTIAL

NDA 8-857/5-009

Wyeth-Ayerst
P.O. Box 8299
Philadelphia, PA 19101-8299

Attention: James J. O'Shaughnessy
Associate Director
U.S. Regulatory Affairs

Dear Mr. O'Shaughnessy:

Reference is made to your supplemental new drug application dated September 21 1981, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenergan (promethazine hydrochloride) Injection.

We acknowledge receipt of your amendments dated May 3, 1988, February 1, March 1, and May 15, 1989, January 7, 1992, and August 6, 1996.

Appendix K

We have completed the review of this supplemental application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) revised as follows.

The following comments are provided regarding the versions of the Phenergan Tubex and Ampul labeling submitted in the August 6, 1996 amendment. Please note that the term "current labeling" refers to these versions.

1. Identical inserts should be utilized for both Phenergan Tubex and Phenergan Ampuls, except for description and usage information specific to the Tubex Sterile Cartridge Unit and the sulfite warning, which is specific to the ampul formulation.

2. The format for the trade name should be "Phenergan (promethazine HCL) Injection" and should be used consistently for both the tubex and ampul products. Within the package inserts, the term "promethazine hydrochloride" or "promethazine HCL" is appropriate for the DESCRIPTION and the CLINICAL PHARMACOLOGY

* * *

10. The WARNINGS section should be modified to read as follows.

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* * *

f. Inadvertent Intra-arterial Injection - Retain verbiage in current label.

* * *

15. The DOSAGE AND ADMINISTRATION section should be modified as follows,

a. The sentence which ends ". . . without some hazard." should be followed by "Not for subcutaneous administration."

b. The sentence which begins "Inadvertent intra-arterial injection . . ." should appear in bold. The statement which follows, regarding rate of administration, should be offset in a separate paragraph.

* * *

16. Regarding the tubex product, the instructions for use refer to a "Tubex injector." This device should be described in the HOW SUPPLIED section.

17. Both Ampuls and Tubex boxes, 25 and 50 mg strength, should describe route of injection as 25 mg - IV or IM, 50 mg - IM only.

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Please submit 16 copies of the printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

If you have any questions, please contact Ms. Beverly Gallauresi, Project Manager, at (301) 827-1054.

Sincerely yours,

s/ John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Appendix K

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

SEP 18 1998

NDA 8-857/S-009

Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

Attention: Nanette E. Holston
Manager
U.S. Regulatory Affairs

Dear Ms. Holston:

Please refer to your supplemental new drug application dated September 21, 1981, received September 21, 1981, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenergan (promethazine hydrochloride) Injection, 25 and 50 mg/mL.

We acknowledge receipt of your submissions dated May 3, 1988, February 1, March 1, and May 15, 1989, January 7, 1992, August 6, 1996, and May 8 and August 21, 1998. Your submission of May 8, 1998, constituted a full response to our February 21, 1997, action letter.

Appendix K

This supplemental new drug application provides for revised labeling.

We have completed the review of this supplemental application, including the draft package insert dated May 8, 1998, and the final printed carton and container labels dated August 21, 1998, and it is approved effective on the date of this letter.

The final printed labeling (FPL) for the package insert must be identical to the draft package insert submitted May 8, 1998.

Please submit 20 copies of the FPL for the package insert as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement 8-857/S-009" Approval of this submission by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of the labeling may be required.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Appendix K

If you have any questions, contact Mr. David Hilfiker, Project Manager, at (301) 827-1046.

Sincerely yours,

s/ John K. Jenkins
John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPENDIX L — CURRENT LABEL

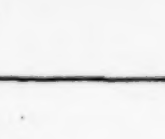
Injection
CI 3727-7

BEST AVAILABLE COPY

Phenergan®
(promethazine HCl)
Injection

DESCRIPTION

Phenergan (promethazine HCl) Injection is a sterile, pyrogen-free solution for deep intramuscular or intravenous administration. Promethazine HCl (10H-phenothiazine-10-ethanamine, *N,N,α*-trimethyl-, monohydrochloride, (±)-) is a racemic compound and has the following structural formula:



$C_{17}H_{20}N_2S \cdot HCl$ MW=320.89

Each mL of the PHENERGAN and PHENERGAN PLAINT PHENTE™ Double Cartridge Units contains either 25 or 50 mg promethazine HCl with 0.1 mg edetate disodium, 0.04 mg sodium sulfoxylate, and more than 5 mg monothioglycerol, and 5 mg phenol as buffer for injection. The pH range is 4.0 to 5.5, buffered with sodium acetate-acetic acid, and it is packed under nitrogen.

Phenergan (promethazine HCl) Injection is a clear, colorless solution. The product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

CLINICAL PHARMACOLOGY

Promethazine HCl is a phenothiazine derivative which possesses antihistaminic, sedative, antimotion-sickness, antiemetic, and anticholinergic effects. Promethazine is a competitive H1 receptor antagonist, but does not block the release of histamine. Structural differences from the neuroleptic phenothiazines result in the relative lack (1/10) of dopamine antagonism properties. In therapeutic doses, promethazine HCl produces an appreciable effect on the cardiovascular system. Clinical effects are generally apparent within 5 minutes of an intravenous injection and within 20 minutes of an intramuscular injection. Duration of action is four to six hours, although effects may persist up to 12 hours. Promethazine HCl is metabolized in the liver, with the formation of promethazine sulfoxide and N-demethylpromethazine being the predominant metabolites appearing in the urine. Following intravenous administration in healthy volunteers, the plasma half-life for promethazine has been reported to range from 9 to 16 hours. The mean plasma half-life for promethazine after intramuscular administration in healthy volunteers has been reported to be 5.0 ± 3.4 hours.

INDICATIONS AND USAGE

Phenergan Injection is indicated for the following conditions:

1. Amelioration of allergic reactions to blood or plasma.
2. As adjunctive to or adjunct to epinephrine and other standard measures after the acute symptoms have been controlled.
3. For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.
4. For sedation and relief of apprehension and to produce light sleep from which the patient can be easily aroused.
5. Active treatment of motion sickness.
6. Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
7. As an adjunct to analgesics for the control of postoperative pain.
8. Preoperative, postoperative, and obstetric (during labor) sedation.
9. Intravenously in special surgical situations, such as repeated bronchoscopy, ophthalmic surgery, and post-vitrectomy patients, with reduced amounts of meperidine or other narcotic analgesic as an adjunct to anesthesia and analgesia.

CONTRAINDICATIONS

Phenergan Injection is contraindicated in comatose states and in patients who have demonstrated an idiosyncrasy or hypersensitivity to antihistamines or other phenothiazines.

Since an extravascular product Phenergan Injection has given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see "WARNINGS—Intravenous and Intra-arterial Injection").

Phenergan Injection should not be given by the subcutaneous route, because of observed irritation has been noted, and necrotic lesions have resulted on rare occasions following subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular injection.

WARNINGS

CNS Depression

Phenergan Injection may impair the mental and physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The impairment may be amplified by concomitant use of other central-nervous-system depressants such as alcohol, barbiturates, narcotics, tranquilizers, general anesthetics, narcotic analgesics, antipsychotics, etc. (see "PRECAUTIONS—Information for Patients").

Lower Seizure Threshold

Phenergan Injection may lower seizure threshold and should be used with caution in persons with seizure disorders or in persons who are using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold.

Bone-Marrow Depression

Phenergan Injection should be used with caution in persons with bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually when Phenergan has been used in association with other known marrow-toxic agents.

Use in Pediatric Patients

PHENERGAN INJECTION IS NOT RECOMMENDED FOR USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PHENERGAN INJECTION TO PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER. ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN PEDIATRIC PATIENTS, AND THEIR USE SHOULD BE LIMITED TO HIGH-DOSED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PHENERGAN INJECTION ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, E.G., ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PHENERGAN INJECTION SHOULD BE AVOIDED IN PEDIATRIC PATIENTS WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME OR OTHER HEPATIC DISEASE.

Excessively large dosages of antihistamines, including Phenergan Injection, in pediatric patients may cause hallucinations, convulsions, and sudden death. In pediatric patients who are usually ill associated with dehydration, there is an increased susceptibility to dystonias with the use of Phenergan Injection.

Intra-arterial Intra-arterial Injection

Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid unintended administration of intravenous intra-arterial injection. Reports compatible with unintended intra-arterial injection of Phenergan Injection usually in combination with other drugs intended for intravenous use, indicated that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation may rarely occur such circumstances. Intravenous injection was intended in all the cases reported but precautions for administration or related assessment of the results were lacking. There is no proven therapeutic management of this syndrome after it occurs, although sympathetic block and hyperbaric oxygen are commonly employed during the acute pathophysiologic sequelae of the results of arterial experiments, with other known arterial injuries. Addition of 25 mg Phenergan Injection with 4 mg of procaine hydrochloride, 1 mg heparin, and 1 mg hydrocortisone per 100 mL of normal saline solution has been reported to prevent these complications.

Phenergan Injection should be given in a concentration not greater than 25 mg per mL and at a rate not to exceed 25 mg per minute. When administering any enteral drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily, in the event that a patient complains of pain during intravenous injection of Phenergan Injection, the injection should be stopped immediately to provide for evaluation of possible arterial puncture or perivascular extravasation.

Visual Inspection

This product is light sensitive and should be inspected before use and discarded if either color or particulate is observed.

Other Considerations

Sedative drugs or CNS depressants should be avoided in patients with a history of drug abuse.

Administration of promethazine has been associated with reported diabetotic jaundice.

PRECAUTIONS

General

Drugs having antihistaminic properties should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction.

Phenergan Injection should be used cautiously in persons with cardiovascular disease or impairment of liver function.

Information for Patients

Phenergan Injection may cause marked drowsiness or impair the mental or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The use of alcohol, narcotics, barbiturates (including barbiturates), general anesthetics, narcotic analgesics, tranquilizers, etc. with Phenergan Injection may additively compound. Patients should be instructed to avoid potential harm in this effect or in other hazardous activities.

Patients should be advised to report any involuntary dystonic movements.

Persistent or worsening pain or burning at the injection site should be reported immediately.

Avoid prolonged exposure to the sun.

Drug Interactions

CNS Depressants - Phenergan Injection may potentiate, additively or synergistically, the sedative effects of central-nervous-system depressants, such as alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. When given concomitantly with Phenergan Injection, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage should be reconsidered if excessive amounts of Phenergan Injection relieve pain in a patient. May lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of the pain.

Epinephrine - Although reversal of the vasopressor effect of epinephrine has not been reported with Phenergan Injection, it is recommended that epinephrine NOT be used in the case of Phenergan Injection overdose.

Antihistamines - Concomitant use of other agents with antihistaminic properties should be undertaken with caution.

Monoamine Oxidase Inhibitors (MAOI) - Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAOI and phenothiazines are used concomitantly. Although such a reaction has not been reported with Phenergan Injection, the possibility should be considered.

Laboratory Test Interactions

The following laboratory tests may be affected in patients who are receiving therapy with Phenergan Injection:

Pregnancy Tests - Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test - An increase in glucose tolerance has been reported in patients receiving promethazine HCl.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of Phenergan Injection, nor are there other sources of human data concerning carcinogenicity, mutagenicity, or impairment of fertility. Phenergan Injection was nonmutagenic in the Ames, Escherichia coli system.

Pregnancy

Teratogenic Effects—Pregnancy Category C

Teratogenic effects have not been demonstrated in rat feeding studies at doses of 6.25 and 12.5 mg/kg (approximately 2.1 and 4.2 times the maximum recommended human daily dose) of Phenergan Injection. Daily doses of 25 mg/kg intramuscularly have been found to produce fetal mortality in rats.

There are no adequate and well-controlled studies of Phenergan Injection in pregnant women. Because animal reproduction studies are not always predictive of human response, Phenergan Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adequate studies to determine the effect of the drug on parturition, lactation and development of the animal neonate have not been conducted.

Abnormogenic Effects

Phenergan Injection flattened within two weeks of delivery may exhibit platelet aggregation in the newborn.

Labor and Delivery

Phenergan Injection may be used alone or as an adjunct to narcotic analgesics during labor (see "DOSAGE AND ADMINISTRATION"). Limited data suggest that use of Phenergan Injection during labor and delivery does not have an appreciable effect on the duration of labor or delivery and does not increase the risk of need for intervention in the newborn. The effect on later growth and development of the newborn is unknown. (See also "Teratogenic Effects.")

Nursing Mothers

It is not known whether Phenergan Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Phenergan Injection is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients under 2 years of age have not been established.

Phenergan Injection should be used with caution in pediatric patients 2 years of age and older (see "WARNINGS—Use in Pediatric Patients").

Use in Geriatric Patients (approximately 60 years or older)

Safety studies with clinical experience have not been performed in geriatric patients. However, the dosage should be reduced for these patients.

ADVERSE REACTIONS

CNS Effects

Drowsiness is the most frequent CNS effect of this drug. Disorientation has also been observed, especially in elderly patients. Confusion, excitation, and hyperreflexia may occur, especially in children. Dizziness, vertigo, blurred vision, fixation of gaze, and tinnitus have been reported.

Cardiovascular Effects

Hypotension, tachycardia, bradycardia, and palpitations have been reported following the use of Phenergan Injection. Rarely, cardiac arrest has occurred following intra-arterial injection of promethazine HCl.

Appendix L

[illegible] ARE [illegible] OF THE AFFECTED

[illegible]

Cardiovascular Effects

[illegible] have been reported, usually in association with surgical procedures and some [illegible] drug therapy.

Allergic Reactions

[illegible] urticaria, pruritus, edema, and anaphylactoid. Angioneurotic edema has been reported.

Other Reported Reactions

Leukopenia and agranulocytosis, usually when Phenergan has been used in association with [illegible] other drugs, have been reported. Thrombophlebitis, necrosis and jaundice of the obstructive type have been associated with the use of Phenergan. The jaundice is usually reversible on discontinuation of the drug. Subcutaneous injection has resulted in tissue necrosis. Acute hemolytic [illegible] has been reported.

Paradoxical Reactions (Overdosage)

Hyperexcitability and convulsive movements, which have been reported in pediatric patients following [illegible] administration of Phenergan injection, may be manifestations of relative overdosage, or [illegible] idiosyncrasy. Caution should be given to the discontinuation of Phenergan injection and to the use of other drugs. Respiratory depression, hypotension, delirium, and agitated behavior have also been reported in spite of these episodes.

OVERDOSAGE

Signs and symptoms of overdosage range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, and unresponsiveness.

Convulsions may be evident, especially in pediatric patients and geriatric patients. Convulsions may rarely occur. A paradoxical reaction has been reported in pediatric patients receiving single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and restlessness.

Recognize the signs and symptoms — dry mouth, [illegible], dilated pupils, flushing, etc., as well as [illegible] exaggerated symptomatic, may occur.

Treatment

Treatment of overdosage is essentially symptomatic and supportive. Only in cases of extreme overdosage or [illegible] satisfactorily do vital signs, including respiration, pulse, blood pressure, temperature, and EKG, need to be monitored. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and intubation of assisted or controlled ventilation. Oxygen may be used to control cyanosis. Analeptics and pressor/vasopressor agents should be avoided. Note that any depressant effects of Phenergan injection are not reversed by naloxone.

Gastric evacuation, which may cause convulsions. The treatment of choice for reducing hypotension is administration of intravenous fluids, supplemented by vasopressors if indicated. In the event that vasopressors are considered for the management of severe hypotension, [illegible] may be required to overcome fluid and vasodilation. The administration of levarterenol or metaraminol should be considered. EPINEPHRINE SHOULD NOT BE USED, since its use in a person with partial parasympathetic blockade may further lower the blood pressure. Extrapyramidal reactions may be treated with antihistaminic preparations, diphenylhydramine, or barbiturates. Oxygen may also be administered. Limited experience with dialysis indicates that it is not helpful.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Do not use Phenergan injection if solution has developed color or contains precipitate.

To avoid the possibility of physical drug incompatibility, consult specialized literature before diluting with any injectable solution or combining with any other medication. Do not use if there is a precipitate or any sign of incompatibility.

Important Notes on Administration

The preferred parenteral route of administration for Phenergan injection is by deep intramuscular injection. The proper intramuscular administration of this product is well-established, but one of the risks is that certain nerve injury, [illegible] postinjection administration.

[illegible] INTRA-ARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see "WARNINGS—Intra-arterial Injection"). SUBCUTANEOUS INJECTION IS CONTRAINDICATED, AS IT MAY RESULT IN TISSUE NECROSIS (see "CONTRAINDICATIONS").

Injection into or near a nerve may result in permanent tissue damage.

When used intravenously, Phenergan injection should be given in concentration no greater than 25 mg/mL at a rate not to exceed 25 mg per minute, it is permissible to inject through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

The TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is suitable for substances to be administered intramuscularly. It is intended for use with injection units specifically manufactured as "needle-less" injection systems. As of the date of this update, the TUBEX BLUNT POINTE is compatible with LifeShield® Protected Needle injection site, InterLink® Injection Site, SmartLine® Injection Site, Clave® Needleless Injection Cap, and SafeSite® valve valve".

The TUBEX® Sterile Cartridge-Needle Unit is suitable for substances to be administered intramuscularly or subcutaneously.

Dosage Guidelines

The average adult dose is 25 mg. This dose may be repeated within two hours if necessary, but repeated therapy, if indicated, should be on the oral route as soon as evening antiemetic permit. After initiation of treatment, dosage should be adjusted to the smallest amount adequate to relieve symptoms. The average adult dose for sedation of elderly patients is 25 mg.

Sedation

In hospitalized adult patients, nighttime sedation may be achieved by a dose of 25 to 50 mg of Phenergan injection.

Nausea and Vomiting

For control of nausea and vomiting, the usual adult dose is 12.5 to 25 mg, not to be repeated more frequently than every four hours. When used for control of postoperative nausea and vomiting, the medication may be administered either intramuscularly or intravenously and dosage of analgesics and barbiturates reduced accordingly.

Preoperative and Postoperative Use

As an adjunct to preoperative or postoperative medication, 25 to 50 mg of Phenergan injection in adults may be combined with appropriately reduced doses of analgesics and [illegible] drugs as desired. Dosage of concomitant analgesic or hypnotic medication should be reduced accordingly.

Obstetrics

Phenergan injection in doses of 50 mg will provide sedation and relieve apprehension in the early stages of labor. When labor is definitely established, 25 to 75 mg (in single doses, 50 mg) Phenergan injection may be given intramuscularly or intravenously with an appropriately reduced dose of any desired narcotic. If necessary, Phenergan injection with a reduced dose of analgesic may be repeated once or twice at four-hour intervals in the course of a normal labor. A maximum total dose of 100 mg of Phenergan injection may be administered during a 24-hour period to patients in labor.

Pediatric Patients

Phenergan injection is not recommended for use in pediatric patients less than two years of age.

In pediatric patients 2 years of age and older, the dosage should not exceed half that of the suggested adult dose. As an adjunct to premedication, the suggested dose is 0.5 mg per lb. of body weight in combination with an appropriately reduced dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug. Antiemetics should not be used in vomiting of unknown etiology in pediatric patients (see "WARNINGS—Use in Pediatric Patients").

HOW SUPPLIED

Phenergan® (promethazine HCl) injection is available in the following dosage strengths in TUBEX® BLUNT POINTE™ Sterile Cartridge Units and Sterile Cartridge-Needle Units, packaged in boxes of 10 TUBEX® as follows:

25 mg per mL, NDC 0008-0410-50, 1 mL box BLUNT POINTE™
25 mg per mL, NDC 0008-0410-01, 1 mL box (22 gauge x 1-1/4 inch needle).
50 mg per mL, NDC 0008-0417-01, 1 mL box (22 gauge x 1-1/4 inch needle).

TUBEX® BLUNT POINTE™ Sterile Cartridge Units and Sterile Cartridge-Needle Units are intended for use with the TUBEX® Injector, which is a reusable plastic injector designed for administration of these products.

Store at room temperature, between 15°C-25°C (59°F-77°F).
Protect from light. Keep carton until time of use.
Do not use if solution has developed color or contains a precipitate.

Also available:

Phenergan Injection is also available in 1 mL ampuls, in packages of 25 ampuls, as follows:

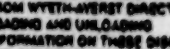
25 mg per mL, NDC 0008-0053-01.
50 mg per mL, NDC 0008-0746-01.

PLEASE NOTE: THE WYETH-AYERST METAL TUBEX HYPODERMIC SYRINGE AND TUBEX FAST-TRAK SYRINGE HAVE BEEN DISCONTINUED AND REPLACED BY THE TUBEX INJECTOR. EXCHANGE OF THESE DISCONTINUED SYRINGES IS AVAILABLE, FREE OF CHARGE, FROM YOUR WYETH-AYERST SALES REPRESENTATIVE, OR FROM WYETH-AYERST DIRECTLY. FOR LOADING AND UNLOADING INFORMATION ON THESE DISCONTINUED SYRINGES, CONTACT THE MEDICAL AFFAIRS DEPARTMENT AT WYETH-AYERST LABORATORIES, P.O. BOX 8299, PHILADELPHIA, PA 19101.

TUBEX® Injector

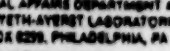
NOTE: The TUBEX Injector is REUSABLE; do not discard.

TUBEX Sterile Cartridge-Needle Unit DIRECTIONS FOR USE:



TUBEX® BLUNT POINTE™ Sterile Cartridge Unit

DIRECTIONS FOR USE:



TUBEX BLUNT POINTE Sterile Cartridge Unit is intended for use with injection units specifically manufactured as "needle-less" injection systems. As of the date of this update, TUBEX BLUNT POINTE Sterile Cartridge Unit is compatible with LifeShield® Protected Needle injection site, InterLink® Injection Site, SmartLine® Injection Site, Clave® Needleless Injection Cap, and SafeSite® valve valve".

Consult manufacturer's recommendations regarding "Directions for Use" of the "needle-less" injection system.

NOTE: USE ASEPTIC TECHNIQUE FOR ALL MANIPULATIONS OF STERILE PARTS.

To load a TUBEX Sterile Cartridge Unit into the TUBEX Injector



1. Turn the ribbed collar to the "OPEN" position until it stops.

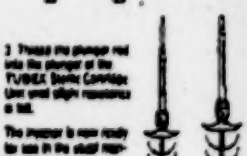


TUBEX Sterile Cartridge-Needle Unit

TUBEX BLUNT POINTE Sterile Cartridge Unit

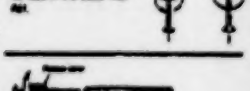
2. Hold the Injector with the open end up and fully insert the TUBEX Sterile Cartridge Unit.

Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.

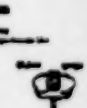


3. Thread the plunger rod into the plunger of the TUBEX Sterile Cartridge Unit until slight resistance is felt.

The Injector is now ready for use in the usual manner.



To load an E.S.I. DOSETTE® Sterile Cartridge-Needle Unit into the TUBEX Injector

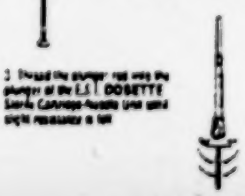


1. Turn the ribbed collar to the "OPEN" position until it stops.



2. Hold the Injector with the open end up and fully insert the E.S.I. DOSETTE Sterile Cartridge-Needle Unit.

Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.



3. Thread the plunger rod into the plunger of the E.S.I. DOSETTE Sterile Cartridge-Needle Unit until slight resistance is felt.



4. Engage the needle tab assembly by pushing the tab down over the barrel cartridge hub. The needle is fully engaged when the lower hub is completely covered.

The Injector is now ready for use in the usual manner.

To administer TUBEX/DOSETTE Sterile Cartridge-Needle Units

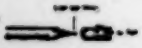
Instead of administering in the same as with conventional syringe. Remove needle cover by grasping it securely, twist and pull. Administer by pushing needle into patient, as per by pushing skin slightly on the plunger, and inject.

To administer TUBEX BLUNT POINTE Sterile Cartridge Units

"Needle-less" IV

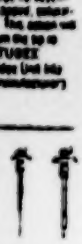
Set administration

A better to administer with conventional syringe.



Remove rubber cover by grasping it securely, twist and pull. "For Safety" notice when securely seats the Luer slip fitting of the TUBEX BLUNT POINTE Sterile Cartridge to accessory with a sterile, individually wrapped, solution of 70% isopropyl alcohol pads. This action will remove the sterile sealing from the tip of [illegible] a right seal. Attached TUBEX BLUNT POINTE Sterile Cartridge Unit into the "needle-less" IV set as per manufacturer's "Directions for Use."

To remove the empty TUBEX/DOSETTE Cartridge Unit and dispose into a vertical disposal container



1. Do not recap the needle point. Disengage the plunger rod

2. Hold the Injector, needle/point down, over a vertical disposal container and loosen the ribbed collar.

TUBEX/DOSETTE Cartridge Unit will drop into the container.



3. Discard the cover.

To remove the empty TUBEX/DOSETTE Cartridge Unit and dispose into a horizontal enclosed disposal container

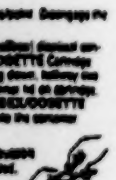
1. Do not recap the needle/point. Disengage the plunger rod

2. Open the horizontal enclosed disposal container. Insert TUBEX/DOSETTE Cartridge Unit, needle/point pointing down, halfway into container. Close the container lid on syringe. Loosen ribbed collar. TUBEX/DOSETTE Cartridge Unit will drop into the container.

3. Discard the cover.

The TUBEX Injector is reusable and should not be discarded.

Used TUBEX/DOSETTE Cartridge Units should not be considered for successive treatment or as multiple-dose containers. They are intended to be used only once and discarded.



NOTE: Any proposed markings on TUBEX/DOSETTE Sterile Cartridge Units are to be used only as a guide in administering dosage. Wyeth-Ayerst does not recommend and will not assume responsibility for the use of any cartridge-needle units or medications safety other than TUBEX or E.S.I. DOSETTE Cartridge Units in the TUBEX Injector.

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